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

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

Indications and Usage (1)	11/2014
Indications and Usage (1)	10/2015
Indications and Usage, Limitations of Use (1)	04/2015
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5)	11/2014
Dosage and Administration (2.1, 2.5)	04/2015
Dosage and Administration (2.1)	10/2015
Contraindications (4)	11/2014
Warnings and Precautions (5.1, 5.2)	04/2015
Warnings and Precautions (5.3, 5.4, 5.5, 5.7)	11/2014

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

OLYSIO is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or 4 infection as a component of a combination antiviral treatment regimen. (1)

Limitations of Use:

- OLYSIO monotherapy is not recommended. (1)
- OLYSIO combination with peginterferon alfa and ribavirin: 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 if HCV genotype 1a with Q80K is detected. (1, 12)
- OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child–Pugh Class B or C). (1)
- 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)

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

- One 150 mg capsule taken once daily with food. (2.1)
- OLYSIO should be administered in combination with other antiviral drugs for the treatment of CHC infection.
- Recommended treatment duration (2.1):
  - OLYSIO with peginterferon alfa and ribavirin in HCV genotype 1 or 4 mono-infected or HCV/human immunodeficiency virus-1 (HIV-1) co-infected patients: 12 weeks, followed by 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on prior response status and presence of HIV-1 co-infection.
  - OLYSIO with sofosbuvir in HCV genotype 1 mono-infected patients:
    - Treatment–naïve or treatment–experienced without cirrhosis: 12 weeks
    - Treatment–naïve or treatment–experienced with cirrhosis: 24 weeks.
- For specific dosage instructions for the other antiviral drugs used in combination with OLYSIO, see their respective prescribing information. (2.1)

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

Capsule: 150 mg (3)

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

All contraindications to other antiviral drugs used with OLYSIO for the treatment of CHC infection also apply to their use in OLYSIO combination treatment. (4)

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

- Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone: 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. Co-administration of amiodarone with OLYSIO in combination with sofosbuvir is not recommended. In patients without alternative treatment options, cardiac monitoring is recommended. (5.1, 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. (5.2)
- 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. (5.4)
- Rash: Rash has been observed during OLYSIO combination therapy. Discontinue OLYSIO if severe rash occurs. (5.5)

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

Most common reported adverse reactions (incidence greater than 20%) (6.1):

- OLYSIO with peginterferon alfa and ribavirin (occurring with at least 3% higher frequency compared to placebo) during first 12 weeks of treatment: rash (including photosensitivity), pruritus and nausea.
- OLYSIO with sofosbuvir during 12 or 24 weeks of treatment: fatigue, headache and nausea.

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----------

- Co-administration of amiodarone with sofosbuvir in combination with OLYSIO may result in serious symptomatic bradycardia. (5.1)
- Co-administration 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. (5.7, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Patients with HCV/HIV-1 co-infection: Safety and efficacy have been studied. (8.11, 14.2)

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

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 OLYSIO Combination Treatment
2.2 Testing Prior to Initiation of OLYSIO in HCV Genotype 1a-Infected Patients
2.3 Discontinuation of Dosing
2.4 Dosage Adjustment or Interruption
2.5 Hepatic Impairment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone
5.2 Hepatic Decompensation and Hepatic Failure
5.3 Risk of Serious Adverse Reactions Associated with Combination Treatment
5.4 Photosensitivity
5.5 Rash
5.6 Sulfa Allergy
5.7 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Potential for OLYSIO to Affect Other Drugs
7.2 Potential for Other Drugs to Affect OLYSIO
7.3 Established and Other Potentially Significant Drug Interactions
7.4 Drugs without Clinically Significant Interactions with OLYSIO
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Race
8.7 Renal Impairment
8.8 Hepatic Impairment
8.9 Other HCV Genotypes
8.10 Liver Transplantation

Reference ID: 3829051

8.11 HCV/HIV-1 Co-infection
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Overview of Clinical Trials
14.2 Treatment with OLYSIO in Combination with Peg-IFN-alfa and RBV
14.3 OLYSIO in Combination with Sofosbuvir
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

Reference ID: 3829051

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OLYSIO® is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) genotype 1 or 4 infection as a component of a combination antiviral treatment regimen.

Limitations of Use:

- OLYSIO monotherapy is not recommended.
- OLYSIO efficacy in combination with peginterferon alfa (Peg-IFN-alfa) and ribavirin (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 (2.2) and Microbiology (12.4)]*. Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.
- OLYSIO is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) *[see Dosage and Administration (2.5), Warnings and Precautions (5.2), Adverse Reactions (6.1, 6.2), Use in Specific Populations (8.8) and Clinical Pharmacology (12.3)]*.
- 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 OLYSIO Combination Treatment

Administer OLYSIO in combination with other antiviral drugs for the treatment of CHC infection. Monitor liver chemistry tests before and during OLYSIO combination therapy *[see Warnings and Precautions (5.2)]*. OLYSIO monotherapy is not recommended. For specific dosing recommendations for the antiviral drugs used in combination with OLYSIO, refer to their respective prescribing information. Administer OLYSIO in combination with either:

- Peg-IFN-alfa and RBV: Table 1 displays the recommended dosage regimen and treatment duration of OLYSIO in combination with Peg-IFN-alfa and RBV. Refer to Table 3 for treatment stopping rules for OLYSIO combination therapy with Peg-IFN-alfa and RBV; or

Reference ID: 3829051

- Sofosbuvir: Table 2 displays the recommended dosage regimen and treatment duration of OLYSIO in combination with sofosbuvir.

The recommended dosage of OLYSIO is one capsule taken orally once daily with food. The capsule should be swallowed as a whole.

Table 1: Recommended Dosage Regimens and Treatment Duration for OLYSIO, Peg-IFN-alfa, and RBV Combination Therapy for Treatment of CHC Infection in HCV Genotype 1 or 4 Mono-infected and HCV/HIV-1 Co-infected Patients

Patient Population	Treatment Regimen and Duration
Treatment-naïve patients and prior relapsers*	
with or without cirrhosis, who are not co-infected with HIV	12 weeks of OLYSIO in combination with Peg-IFN-alfa and RBV followed by an additional 12 weeks of Peg-IFN-alfa and RBV (total treatment duration of 24 weeks)†
without cirrhosis, who are co-infected with HIV	
with cirrhosis, who are co-infected with HIV	12 weeks of OLYSIO in combination with Peg-IFN-alfa and RBV followed by an additional 36 weeks of Peg-IFN-alfa and RBV (total treatment duration of 48 weeks)†
Prior non-responders (including partial‡ and null responders#), with or without cirrhosis, with or without HIV co-infection	12 weeks of OLYSIO in combination with Peg-IFN-alfa and RBV followed by an additional 36 weeks of Peg-IFN-alfa and 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 $\geq 2 \log_{10}$ 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 $< 2 \log_{10}$ reduction in HCV RNA from baseline at Week 12 during prior IFN-based therapy *[see Clinical Studies (14)]*.

Table 2: Recommended Dosage Regimen and Treatment Duration for OLYSIO and Sofosbuvir Combination Therapy for Treatment of CHC Infection in HCV Genotype 1 Mono-infected Patients

Patient Population	Treatment Regimen and Duration
Treatment-naïve and treatment-experienced* patients without cirrhosis	12 weeks of OLYSIO + sofosbuvir
Treatment-naïve and treatment-experienced* patients with cirrhosis	24 weeks of OLYSIO + sofosbuvir

* Treatment-experienced patients include prior relapsers, prior partial responders and prior null responders who failed prior IFN-based therapy.

2.2 Testing Prior to Initiation of OLYSIO in HCV Genotype 1a-Infected Patients

Prior to initiation of treatment with OLYSIO 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. Prior to

Reference ID: 3829051

initiation of treatment with OLYSIO with sofosbuvir, screening patients infected with HCV genotype 1a for the presence of virus with the NS3 Q80K polymorphism is not strongly recommended but may be considered *[see Indications and Usage (1)]*.

2.3 Discontinuation of Dosing

Use 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 ≥ 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.

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)

Use with Sofosbuvir

No treatment stopping rules apply to the combination of OLYSIO with sofosbuvir *[see Clinical Studies (14)]*.

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.

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 drugs used in combination with OLYSIO for the treatment of CHC infection are permanently discontinued for any reason, OLYSIO should also be discontinued.

Reference ID: 3829051

2.5 Hepatic Impairment

OLYSIO is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) *[see Use in Specific Populations (8.8)]*. There have been postmarketing reports of hepatic decompensation, hepatic failure, and death in patients with advanced or decompensated cirrhosis receiving OLYSIO combination therapy *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*. Simeprevir exposures are increased in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) *[see Clinical Pharmacology (12.3)]*.

In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including increased bilirubin, rash and photosensitivity *[see Adverse Reactions (6.1)]*.

OLYSIO in combination with Peg-IFN-alfa and RBV is contraindicated in patients with decompensated cirrhosis (moderate or severe hepatic impairment) *[see Peg-IFN-alfa prescribing information]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 150 mg, white and marked with “TMC435 150” in black ink.

4 CONTRAINDICATIONS

There are no specific contraindications to OLYSIO.

The contraindications to other antiviral drugs administered with OLYSIO for the treatment of CHC infection also apply to OLYSIO combination treatment. Prescribers should consult the complete prescribing information for these drugs for a description of contraindications.

If OLYSIO is administered with Peg-IFN-alfa and RBV, the contraindications for use of Peg-IFN-alfa and RBV also apply to this combination regimen. Refer to the prescribing information for Peg-IFN-alfa and RBV for a list of all contraindications.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is co-administered with sofosbuvir in combination with another HCV direct acting antiviral, including OLYSIO. A fatal cardiac arrest was reported in a patient receiving 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 co-administration

Reference ID: 3829051

of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this bradycardia effect is unknown.

Co-administration 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 co-administered OLYSIO and sofosbuvir:

- Counsel patients about the risk of serious symptomatic bradycardia
- Cardiac monitoring in an in-patient setting for the first 48 hours of co-administration 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)]*.

5.2 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 peginterferon alfa and ribavirin 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 Class 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

Reference ID: 3829051

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

5.3 Risk of Serious Adverse Reactions Associated with Combination Treatment

OLYSIO should be used in combination with other antiviral drugs for the treatment of CHC infection. Therefore, 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.

5.4 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.

5.5 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

Reference ID: 3829051

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.

5.6 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.

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

Co-administration 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

OLYSIO should be 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 drug reactions (ADRs) are discussed in detail in another section of the labeling:

- Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone *[see Warnings and Precautions (5.1) and Drug Interactions (7.3)]*
- Hepatic Decompensation and Hepatic Failure *[see Warnings and Precautions (5.2)]*
- Photosensitivity *[see Warnings and Precautions (5.4)]*
- Rash *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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

Reference ID: 3829051

Adverse Reactions when Used 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 who were treatment-naïve or who had previously relapsed following interferon therapy with or without RBV is based on pooled data from three Phase 3 trials *[see Clinical Studies (14)]*. 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.

The following table 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 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 (see Table 4).

Table 4: 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 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 CHC Infection[*] (Pooled Phase 3 Trials[†])

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.

Reference ID: 3829051

Rash and Photosensitivity

In the Phase 3 clinical trials, 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 Grade 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.

Dyspnea

During the 12 weeks of treatment with OLYSIO, 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

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 5.

Reference ID: 3829051

Table 5: Laboratory Abnormalities (WHO Worst Toxicity Grades 1 to 4) Observed at a Higher Incidence in OLYSIO-Treated Subjects (Pooled Phase 3 Trials[*]; 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.

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

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

Adverse Reactions when Used with Sofosbuvir

In the COSMOS trial, the most common (> 10%) adverse reactions reported during 12 weeks treatment with OLYSIO in combination with sofosbuvir without RBV were fatigue (25%), headache (21%), nausea (21%), insomnia (14%) and pruritus (11%). Rash and photosensitivity were reported in 11% and 7% of subjects, respectively. During 24 weeks treatment with OLYSIO in combination with sofosbuvir, dizziness (16%), and diarrhea (16%) were also commonly reported.

Reference ID: 3829051

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 initiate treatment with sofosbuvir in combination with another HCV direct acting antiviral, including OLYSIO *[see Warnings and Precautions (5.1) and Drug Interactions (7.3)]*.

Hepatobiliary Disorders: hepatic decompensation, hepatic failure *[see Warnings and Precautions (5.2)]*.

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. Co-administration of OLYSIO with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs (see Table 6). Simeprevir does not affect CYP2C9, CYP2C19 or CYP2D6 *in vivo*.

Simeprevir inhibits OATP1B1/3 and P-glycoprotein (P-gp) transporters. Co-administration of OLYSIO with drugs that are substrates for OATP1B1/3 and P-gp transport may result in increased plasma concentrations of such drugs (see Table 6).

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. Co-administration of OLYSIO with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir. Co-administration with moderate or strong inducers of CYP3A may significantly reduce the plasma exposure of simeprevir and lead to loss of efficacy (see Table 6). Therefore, co-administration of OLYSIO with substances that are moderate or strong inducers or inhibitors of CYP3A is not recommended *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*.

7.3 Established and Other Potentially Significant Drug Interactions

Table 6 shows the established and other potentially significant drug interactions based on which alterations in dose or regimen of OLYSIO and/or co-administered drug may be recommended. Drugs that are not recommended for co-administration with OLYSIO are also included in Table 6. For information regarding the magnitude of interaction, see Tables 7 and 8 *[see Clinical Pharmacology (12.3)]*.

Reference ID: 3829051

Table 6: 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	Co-administration of amiodarone with OLYSIO in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If co-administration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.1), Adverse Reactions (6.2)]*.
	↑ 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. Concomitant use of OLYSIO with amiodarone when given orally may result in mild increases in amiodarone concentrations due to intestinal CYP3A4 inhibition by simeprevir.
Digoxin*	↑ digoxin	Concomitant use of OLYSIO with digoxin resulted in increased concentrations of digoxin due to inhibition of P-gp by simeprevir. Routine therapeutic drug monitoring of digoxin concentrations is acceptable.
Oral administration Disopyramide Flecainide Mexiletine Propafenone Quinidine	↑ antiarrhythmics	Concomitant use of OLYSIO with these antiarrhythmics when given orally may result in mild increases in concentrations of these antiarrhythmics due to intestinal CYP3A4 inhibition by simeprevir. Therapeutic drug monitoring for these antiarrhythmics, if available, is recommended when co-administered with OLYSIO.
Anticonvulsants		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓ simeprevir	Concomitant use of OLYSIO with carbamazepine, oxcarbazepine, phenobarbital or phenytoin may result in significantly decreased plasma concentrations of simeprevir due to strong CYP3A induction by these anticonvulsants. This may result in loss of therapeutic effect of OLYSIO. Co-administration of OLYSIO with these anticonvulsants is not recommended.
Anti-infectives		
Antibiotics (systemic administration): Erythromycin*	↑ simeprevir ↑ erythromycin	Concomitant use of OLYSIO with erythromycin resulted in significantly increased plasma concentrations of both erythromycin and simeprevir due to inhibition of CYP3A and P-gp by both erythromycin and simeprevir. Co-administration of OLYSIO with systemic erythromycin is not recommended.

Reference ID: 3829051

Antibiotics (systemic administration): Clarithromycin Telithromycin	↑ simeprevir	Concomitant use of OLYSIO with clarithromycin or telithromycin may result in increased plasma concentrations of simeprevir due to CYP3A inhibition by these antibiotics. Co-administration of OLYSIO with systemic clarithromycin or telithromycin is not recommended.
Antifungals (systemic administration): Itraconazole Ketoconazole Posaconazole	↑ simeprevir	Concomitant use of OLYSIO with systemic itraconazole, ketoconazole or posaconazole may result in significantly increased plasma concentrations of simeprevir due to strong CYP3A inhibition by these antifungals. Co-administration of OLYSIO with systemic itraconazole, ketoconazole or posaconazole is not recommended.
Antifungals (systemic administration): Fluconazole Voriconazole	↑ simeprevir	Concomitant use of OLYSIO with systemic fluconazole or voriconazole may result in increased plasma concentrations of simeprevir due to mild to moderate CYP3A inhibition by these antifungals. Co-administration of OLYSIO with systemic fluconazole or voriconazole is not recommended.
Antimycobacterials: Rifampin*† Rifabutin Rifapentine	↓ simeprevir ↔ rifampin, rifabutin, rifapentine	Concomitant use of OLYSIO with rifampin, rifabutin or rifapentine may result in significantly decreased plasma concentrations of simeprevir due to CYP3A4 induction by these antimycobacterials. This may result in loss of therapeutic effect of OLYSIO. Co-administration of OLYSIO with rifampin, rifabutin or rifapentine is not recommended.
Calcium Channel Blockers (oral administration)		
Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Nisoldipine Verapamil	↑ calcium channel blockers	Concomitant use of OLYSIO with orally administered calcium channel blockers may result in increased plasma concentrations of calcium channel blockers due to intestinal CYP3A4 and/or P-gp inhibition by simeprevir. Clinical monitoring of patients is recommended when OLYSIO is co-administered with orally administered calcium channel blockers.
Corticosteroids		
Systemic Dexamethasone	↓ simeprevir	Concomitant use of OLYSIO with systemic dexamethasone may result in decreased plasma concentrations of simeprevir due to moderate induction of CYP3A4 by dexamethasone. This may result in loss of therapeutic effect of OLYSIO. Co-administration of OLYSIO with systemic dexamethasone is not recommended.
Gastrointestinal Products		
Propulsive: Cisapride	↑ cisapride	Cisapride has the potential to cause cardiac arrhythmias. Concomitant use of OLYSIO with cisapride may result in increased plasma concentrations of cisapride due to intestinal CYP3A4 inhibition by simeprevir. Co-administration of OLYSIO with cisapride is not recommended.
Herbal Products		

Reference ID: 3829051

Milk thistle (*Silybum marianum*)	↑ simeprevir	Concomitant use of OLYSIO with milk thistle may result in increased plasma concentrations of simeprevir due to CYP3A inhibition by milk thistle. Co-administration of OLYSIO with milk thistle is not recommended.
St. John's wort (*Hypericum perforatum*)	↓ simeprevir	Concomitant use of OLYSIO with products containing St. John's wort may result in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by St. John's wort. This may result in loss of therapeutic effect of OLYSIO. Co-administration of OLYSIO with products containing St. John's wort is not recommended.
HIV Products		
Cobicistat-containing product	↑ simeprevir	Concomitant use of OLYSIO and a cobicistat-containing product may result in significantly increased plasma concentrations of simeprevir due to strong CYP3A inhibition by cobicistat. Co-administration of OLYSIO with a cobicistat-containing product is not recommended.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): Efavirenz[*]	↓ simeprevir ↔ efavirenz	Concomitant use of OLYSIO with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz. This may result in loss of therapeutic effect of OLYSIO. Co-administration of OLYSIO with efavirenz is not recommended.
Other NNRTIs (Delavirdine, Etravirine, Nevirapine)	↑ or ↓ simeprevir	Concomitant use of OLYSIO with delavirdine, etravirine or nevirapine may result in altered plasma concentrations of simeprevir due to CYP3A inhibition (delavirdine) or induction (etravirine and nevirapine) by these drugs. Co-administration of OLYSIO with delavirdine, etravirine or nevirapine is not recommended.
Protease Inhibitors (PIs): Darunavir/ritonavir[*‡]	↑ simeprevir ↑ darunavir	Concomitant use of OLYSIO with darunavir/ritonavir resulted in increased plasma concentrations of simeprevir due to CYP3A inhibition by darunavir/ritonavir. Co-administration of darunavir/ritonavir and OLYSIO is not recommended.
Protease Inhibitors (PIs): Ritonavir[*#]	↑ simeprevir	Concomitant use of OLYSIO with ritonavir resulted in significantly increased plasma concentrations of simeprevir due to strong CYP3A inhibition by ritonavir. Co-administration of OLYSIO with ritonavir is not recommended.
Other ritonavir-boosted or unboosted HIV PIs, e.g., Atazanavir, Fosamprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir	↑ or ↓ simeprevir	Concomitant use of OLYSIO with ritonavir-boosted or unboosted HIV PIs may result in altered plasma concentrations of simeprevir due to CYP3A inhibition or induction by these HIV PIs. Co-administration of OLYSIO with any HIV PI, with or without ritonavir is not recommended.
HMG CO-A Reductase Inhibitors		

Reference ID: 3829051

Rosuvastatin*	↑ rosuvastatin	Concomitant use of OLYSIO with rosuvastatin resulted in increased plasma concentrations of rosuvastatin due to inhibition of OATP1B1 by simeprevir. Initiate rosuvastatin therapy with 5 mg once daily. The rosuvastatin dose should not exceed 10 mg daily when co-administered with OLYSIO.
Atorvastatin*	↑ atorvastatin	Concomitant use of OLYSIO with atorvastatin resulted in increased plasma concentrations of atorvastatin due to inhibition of OATP1B1 and/or CYP3A4 by simeprevir. Use the lowest necessary dose of atorvastatin, but do not exceed a daily dose of 40 mg when co-administering with OLYSIO.
Simvastatin*	↑ simvastatin	Concomitant use of OLYSIO with simvastatin resulted in increased plasma concentrations of simvastatin due to inhibition of OATP1B1 and/or CYP3A4 by simeprevir. Titrate the simvastatin dose carefully and use the lowest necessary dose of simvastatin while monitoring for safety when co-administered with OLYSIO.
Pitavastatin Pravastatin Lovastatin	↑ pitavastatin, pravastatin, lovastatin	Concomitant use of OLYSIO with pitavastatin, pravastatin or lovastatin has not been studied. The dose of pitavastatin, pravastatin or lovastatin should be titrated carefully and the lowest necessary dose should be used while monitoring for safety when co-administered with OLYSIO.
Immunosuppressants		
Cyclosporine*	↑ cyclosporine ↑ simeprevir§	Concomitant use of OLYSIO with cyclosporine resulted in significantly increased plasma concentrations of simeprevir due to inhibition of OATP1B1, P-gp and CYP3A by cyclosporine. It is not recommended to co-administer OLYSIO with cyclosporine.
Sirolimus	↑ or ↓ sirolimus	Concomitant use of OLYSIO and sirolimus may result in mildly increased or decreased plasma concentrations of sirolimus. Routine monitoring of blood concentrations of sirolimus is acceptable.
Phosphodiesterase Type 5 (PDE-5) Inhibitors		
Sildenafil Tadalafil Vardenafil	↑ PDE-5 inhibitors	Concomitant use of OLYSIO with PDE-5 inhibitors may result in mild increases in concentrations of PDE-5 inhibitors due to intestinal CYP3A4 inhibition by simeprevir. No dose adjustment is required when OLYSIO is co-administered with doses of sildenafil, tadalafil or vardenafil indicated for the treatment of erectile dysfunction. Dose adjustment of the PDE-5 inhibitor may be required when OLYSIO is co-administered with sildenafil or tadalafil administered chronically at doses used for the treatment of pulmonary arterial hypertension. Consider starting with the lowest dose of the PDE-5 inhibitor and increase as needed, with clinical monitoring as appropriate.
Sedatives/Anxiolytics		

Reference ID: 3829051

Midazolam* (oral administration)	↑ midazolam	Concomitant use of OLYSIO with orally administered midazolam resulted in increased plasma concentrations of midazolam due to mild inhibition of intestinal CYP3A4 by simeprevir. Caution is warranted when this drug, with a narrow therapeutic index, is co-administered with OLYSIO via the oral route.
Triazolam (oral administration)	↑ triazolam	Concomitant use of OLYSIO with orally administered triazolam may result in mild increases in concentrations of triazolam due to intestinal CYP3A4 inhibition by simeprevir. Caution is warranted when this drug, with a narrow therapeutic index, is co-administered with OLYSIO via the oral route.

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 7* and *8]*.

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

‡ The dose of OLYSIO in this interaction study was 50 mg when co-administered 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 co-administered in combination with ritonavir 100 mg given twice daily.

§ Studied in combination with an investigational drug 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 6, 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, dextromethorphan, escitalopram, ethinyl estradiol/norethindrone, methadone, midazolam (intravenous administration), omeprazole, raltegravir, rilpivirine, sofosbuvir, tacrolimus, tenofovir disoproxil fumarate, and warfarin.

No clinically relevant drug-drug interaction is expected when OLYSIO is co-administered with antacids, azithromycin, bedaquiline, the corticosteroids budesonide, fluticasone, methylprednisolone, and prednisone, dolutegravir, fluvastatin, 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

OLYSIO must be administered in combination with other antiviral drugs *[see Dosage and Administration (2.1)]*. Refer to prescribing information of the drugs used in combination with OLYSIO for information regarding use in pregnancy.

Reference ID: 3829051

Pregnancy Category C

Risk Summary

Adequate and well-controlled trials with OLYSIO have not been conducted in pregnant women. In animal reproduction studies with simeprevir, embryofetal developmental toxicity was observed at drug exposures higher than human exposure at the recommended clinical dose. OLYSIO should be used during pregnancy only if the potential benefit justifies the potential risk. Female patients of childbearing potential should use an effective contraceptive method.

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

Animal Data

Simeprevir showed no teratogenicity in rats and mice at exposures 0.5 times (in rats) and 6 times (in mice) the mean area under the plasma concentration time curve (AUC) in humans at the recommended dose of 150 mg once daily.

In a mouse embryofetal study at doses up to 1000 mg/kg, simeprevir resulted in early and late *in utero* fetal losses and early maternal deaths at an exposure approximately 6 times higher than the mean AUC in humans at the recommended 150 mg daily dose. Significantly decreased fetal weights and an increase in fetal skeletal variations were seen at exposures approximately 4 times higher than the mean AUC in humans at the recommended daily dose.

In a rat pre- and postnatal study, maternal animals were exposed to simeprevir during gestation and lactation at doses up to 1000 mg/kg/day. In pregnant rats, simeprevir resulted in early deaths at 1000 mg/kg/day corresponding to exposures similar to the mean AUC in humans at the recommended 150 mg once daily dose. Significant reduction in body weight gain was seen at an exposure 0.7 times the mean AUC in humans at the recommended 150 mg once daily dose. 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 a maternal exposure similar to the mean AUC in humans at the recommended 150 mg once daily dose. Subsequent survival, behavior and reproductive capacity were not affected.

8.3 Nursing Mothers

It is not known whether OLYSIO or its metabolites are present in human breast milk. When administered to lactating rats, simeprevir was detected in plasma of suckling rats likely due to excretion of simeprevir via milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to

Reference ID: 3829051

discontinue nursing or discontinue treatment with OLYSIO, taking into account the importance of the therapy to the mother.

If OLYSIO is administered in a regimen containing RBV, the information for RBV with regard to nursing mothers also applies to this combination regimen *[see prescribing information for RBV]*.

8.4 Pediatric Use

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

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 dose adjustment of OLYSIO is required in geriatric patients *[see Clinical Pharmacology (12.3)]*.

8.6 Race

Patients of East Asian ancestry exhibit higher simeprevir exposures *[see Clinical Pharmacology (12.3)]*. In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity *[see Adverse Reactions (6.1)]*. There are insufficient safety data to recommend an appropriate dose for patients of East Asian ancestry. The potential risks and benefits of OLYSIO should be carefully considered prior to use in patients of East Asian ancestry.

8.7 Renal Impairment

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

The safety and efficacy of OLYSIO have not been established in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

Reference ID: 3829051

OLYSIO is not recommended for patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) *[see Dosage and Administration (2.5)]*. There have been postmarketing reports of hepatic decompensation, hepatic failure, and death in patients with advanced or decompensated cirrhosis receiving OLYSIO combination therapy *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*. Simeprevir exposures are increased in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) *[see Clinical Pharmacology (12.3)]*. In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including increased bilirubin, rash and photosensitivity *[see Adverse Reactions (6.1)]*.

Refer to the prescribing information for the antiviral drug(s) used in combination with OLYSIO regarding their use in patients with hepatic impairment. The combination of OLYSIO with Peg-IFN-alfa and RBV is contraindicated in patients with decompensated cirrhosis (moderate or severe hepatic impairment).

8.9 Other HCV Genotypes

The safety and efficacy of OLYSIO have not been established in patients infected with other HCV genotypes.

8.10 Liver Transplantation

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

8.11 HCV/HIV-1 Co-infection

No dose adjustment of OLYSIO is required in HCV/HIV-1 co-infected patients *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*. For dosing recommendations in HCV/HIV-1 co-infected patients, see *Dosage and Administration (2.1)*. For information on the safety profile of OLYSIO in combination with Peg-IFN-alfa and RBV in patients with HCV genotype 1/HIV-1 co-infection, see *Adverse Reactions (6.1)*.

For information on interactions with antiretroviral agents, see *Warning and Precautions (5.7) and Drug Interactions (7)*.

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.

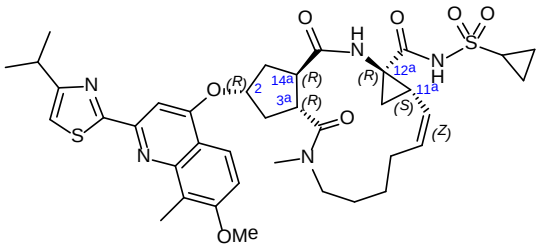
Simeprevir is highly protein-bound; therefore, dialysis is unlikely to result in significant removal of simeprevir *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

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

Reference ID: 3829051

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)]*.

12.2 Pharmacodynamics

<u>Cardiac Electrophysiology</u>

The effect of simeprevir at the recommended dose of 150 mg once daily and 350 mg (at 2.3 times the recommended dosage) once daily for 7 days on the QT interval was evaluated in a randomized, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg once daily), 4-way cross-over study in 60 healthy subjects. No meaningful changes in QTc interval were observed at either the recommended dose of 150 mg once daily or the dose of 350 mg (2.3 times the recommended dosage) once daily.

Reference ID: 3829051

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 co-administration of simeprevir with Peg-IFN-alfa and RBV compared with administration of simeprevir alone. In HCV-infected subjects, the mean steady-state predose plasma concentration was 1936 ng/mL (standard deviation: 2640) and the mean steady-state AUC_{24} was 57469 ng.h/mL (standard deviation: 63571).

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. Due to increased bioavailability, OLYSIO should be administered with food. The type of food does not affect exposure to simeprevir.

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 system. Involvement of CYP2C8 and CYP2C19 cannot be excluded. Co-administration of OLYSIO with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir, and co-administration with

Reference ID: 3829051

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. No dose adjustment of OLYSIO is required in geriatric patients *[see Use in Specific Populations (8.5)]*.

Renal Impairment

Renal elimination of simeprevir is negligible. 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). Based on the observed and expected changes in simeprevir exposure, no dose adjustment of OLYSIO is needed in patients with mild, moderate or severe renal impairment. The safety and efficacy of OLYSIO have not been studied in HCV-infected patients with severe renal impairment or end-stage renal disease, including patients requiring dialysis *[see Use in Specific Populations (8.7)]*.

In a population pharmacokinetic analysis of mild or moderate renally impaired HCV-infected subjects treated with OLYSIO 150 mg once daily, creatinine clearance

Reference ID: 3829051

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.

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

Refer to the prescribing information for the antiviral drugs used in combination with OLYSIO regarding their use in patients with renal impairment.

Hepatic Impairment

Simeprevir is primarily metabolized by the liver. 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 Class B) and 5.2-fold higher in HCV-uninfected subjects with severe hepatic impairment (Child-Pugh Class C).

No dose adjustment of OLYSIO is necessary in patients with mild hepatic impairment (Child-Pugh Class A).

The safety and efficacy of OLYSIO have not been established in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C).

OLYSIO is not recommended for use in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) *[see Dosage and Administration (2.5), Warnings and Precautions (5.2) and Use in Specific Populations (8.8)]*.

In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including increased bilirubin, rash and photosensitivity *[see Adverse Reactions (6.1)]*.

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

Refer to the prescribing information for the antiviral drugs used in combination with OLYSIO regarding their use in patients with hepatic impairment.

Gender, Body Weight, Body Mass Index

No dose adjustment is necessary based on gender, body weight or body mass index. These characteristics have no clinically meaningful relevant effect on the pharmacokinetics of simeprevir based on a population pharmacokinetic analysis of HCV-infected subjects treated with OLYSIO.

Reference ID: 3829051

Race

Based on results from studies in HCV-uninfected subjects and HCV-infected subjects, simeprevir exposures are higher in Asians compared to Caucasians. In the Phase 3 trials, the mean simeprevir plasma exposure in Asian subjects (n=14) was 3.4-fold higher than in the pooled Phase 3 population. In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity. There are insufficient safety data to recommend an appropriate dose for patients of East Asian ancestry. The potential risks and benefits of OLYSIO should be carefully considered prior to use in patients of East Asian ancestry *[see Use in Specific Populations (8.6)]*.

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

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 (5.7) 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 and BSEP. The 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, co-administration of OLYSIO with moderate or strong inhibitors of CYP3A may significantly increase the plasma exposure of simeprevir and co-administration 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

Reference ID: 3829051

co-administered or drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of other drugs on the C_{max}, AUC, and C_{min} values of simeprevir are summarized in Table 7 (effect of other drugs on OLYSIO). The effect of co-administration of OLYSIO on the C_{max}, AUC, and C_{min} values of other drugs are summarized in Table 8 (effect of OLYSIO on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7).*

Table 7: Drug Interactions: Pharmacokinetic Parameters for Simeprevir in the Presence of Co-administered Drugs

Co-administered 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	9	↑	4.74 (3.12-7.18)	5.81 (3.56-9.48)	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	11	↑	1.79 (1.22-2.62)	1.85 (1.18-2.91)	NA
Anti-HCV Drug							
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)
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. Interim data from a Phase 2 trial in combination with an investigational drug and RBV in HCV-infected post-liver transplant patients.

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

\# Comparison based on historic controls. The interaction between simeprevir and sofosbuvir was evaluated in a pharmacokinetic substudy within a Phase 2 trial.

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

Reference ID: 3829051

Table 8: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of OLYSIO

Co-administered Drug	Dose (mg) and Schedule		N	Effect on PK*	LS Mean Ratio (90% CI) of Co-Administered 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), co-administered 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., individualised 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)
Norethindrone (NE), co-administered 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

Reference ID: 3829051

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							
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 OLYSIO and the drug was evaluated in a pharmacokinetic study in opioid-dependent adults on stable methadone maintenance therapy.

[‡] Comparison based on historic controls. The interaction between simeprevir and sofosbuvir was evaluated in a pharmacokinetic substudy within a Phase 2 trial.

[#] Primary circulating metabolite of sofosbuvir.

[§] The dose of OLYSIO in this interaction study was 50 mg when co-administered in combination with darunavir/ritonavir which is lower than the recommended 150 mg dose.

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

Reference ID: 3829051

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 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, 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 9). 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

Reference ID: 3829051

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 9). In HCV genotype 1a with a baseline Q80K amino acid polymorphism, an emerging R155K substitution was observed most frequently at failure.

Table 9: 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)	61 (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.

In the COSMOS trial in HCV genotype 1-infected subjects treated with OLYSIO in combination with sofosbuvir (without or with RBV), virus from 5 out of 6 (83%) subjects with relapse had emerging NS3 amino acid substitutions R155K or D168E. No emerging NS5B amino acid substitutions associated with sofosbuvir resistance were observed.

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

Reference ID: 3829051

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 (14.2)]*.

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 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 (RESTORE).

Cross-Resistance

Cross-resistance is expected among NS3/4A protease inhibitors. Some of the treatment-emergent virus detected in OLYSIO-treated subjects who did not achieve SVR in clinical trials, including virus expressing R155K, which emerged frequently, and I170T, which emerged infrequently, have been shown to be less susceptible to the NS3/4A protease inhibitors, boceprevir and/or telaprevir.

The most frequently occurring boceprevir or telaprevir treatment-emergent viruses that are expected to impact subsequent treatment with OLYSIO include variants expressing NS3 R155K, A156T, or A156V. Virus expressing the NS3 amino substitutions V36A or G and I170A or T, which displayed slight shifts in susceptibility to simeprevir in replicon

Reference ID: 3829051

cultures, may emerge in patients who do not achieve SVR with boceprevir or telaprevir, and may therefore also impact subsequent treatment with OLYSIO. Failure to achieve SVR with simeprevir does not select virus that is cross-resistant to sofosbuvir or vice versa.

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 10 and 11). 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 10).

Table 10: 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 (Trials 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).

Table 11: SVR12 Rates by *IL28B* rs12979860 Genotype in Adult Patients Receiving OLYSIO 150 mg Once Daily in Combination with Peg-IFN-alfa and RBV (Trials 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.

Reference ID: 3829051

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 approximately 0.2 times the mean AUC in humans.

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 in a combination regimen containing sofosbuvir, refer to the prescribing information for sofosbuvir for information on animal toxicology.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy of OLYSIO in combination with Peg-IFN-alfa and RBV in patients with HCV genotype 1 infection was evaluated in two Phase 3 trials in treatment-naïve subjects (trials QUEST 1 and QUEST 2), 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 (trial C212).

Reference ID: 3829051

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).

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. Subjects in these trials had compensated liver disease (including cirrhosis), HCV RNA of at least 10000 IU/mL, and liver histopathology consistent with CHC 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 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.

The efficacy of OLYSIO in combination with sofosbuvir without or with RBV was evaluated in a Phase 2 trial (COSMOS) in HCV genotype 1 infected prior null responders with METAVIR fibrosis score F0-F4 or treatment-naïve subjects with METAVIR fibrosis score F3-F4 and compensated liver disease.

SVR was defined as HCV RNA not detected 24 weeks after planned end of treatment (SVR24) in the ASPIRE trial and was defined as HCV RNA lower than 25 IU/mL detected or not detected 12 weeks after the planned end of treatment (SVR12) in the COSMOS and Phase 3 trials.

14.2 Treatment with 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,

Reference ID: 3829051

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

Table 12: Response Rates in Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection (Pooled Data QUEST 1 and QUEST 2)

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 all 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.

Reference ID: 3829051

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-eight percent (78%; 404/521) 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 13 shows the SVR rates by METAVIR fibrosis score.

Table 13: SVR12 Rates by METAVIR Fibrosis Score in Treatment-Naïve Adult Subjects with HCV Genotype 1 Infection (Pooled Data QUEST 1 and QUEST 2)

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).

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 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

Reference ID: 3829051

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%).

Table 14 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 14: Response Rates 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 all 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%; 200/260) 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 15 shows the SVR rates by METAVIR fibrosis score.

Table 15: 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)

Reference ID: 3829051

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.

The ASPIRE trial was a randomized, double-blind, placebo-controlled, 7-arm, 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). Subjects received 12, 24 or 48 weeks of 100 mg or 150 mg OLYSIO in combination with 48 weeks of Peg-IFN-alfa-2a and RBV, or 48 weeks of placebo in combination with 48 weeks of Peg-IFN-alfa-2a and RBV.

Demographics and baseline characteristics were balanced between the OLYSIO and placebo treatment groups. The 462 subjects enrolled in the ASPIRE trial had a median age of 50 years (range: 20 to 69 years; with 3% above 65 years); 67% were male; 93% were White, 5% Black or African American, and 2% Asian; 25% had a BMI greater than or equal to 30 kg/m^2; 86% had HCV RNA levels greater than 800000 IU/mL; 63% had METAVIR fibrosis score F0, F1, or F2, 19% METAVIR fibrosis score F3, and 18% METAVIR fibrosis score F4 (cirrhosis); 41% had HCV genotype 1a, and 58% HCV genotype 1b; 18% had *IL28B* CC genotype, 65% *IL28B* CT genotype, and 18% *IL28B* TT genotype (information available for 328 subjects); 12% of the overall population and 27% 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. One hundred ninety-nine subjects received OLYSIO 150 mg once daily (pooled analysis) of which 66 subjects received OLYSIO for 12 weeks and 66 subjects received placebo in combination with Peg-IFN-alfa and RBV.

Table 16 shows the response rates for the OLYSIO and placebo treatment groups in prior relapsers, prior partial responders and prior null responders.

Table 16: Response Rates in Prior Partial and Null Responders with HCV Genotype 1 Infection who Failed Prior Peg-IFN-alfa and RBV Therapy (ASPIRE Trial)

Response Rates	**150 mg OLYSIO 12 Weeks + PR N=66 % (n/N)**	**Pooled 100 mg and 150 mg OLYSIO 12 Weeks + PR N=132 % (n/N)**	**Placebo + PR N=66 % (n/N)**
SVR24			
Prior relapsers	77 (20/26)	83 (44/53)	37 (10/27)
Prior partial responders	65 (15/23)	67 (31/46)	9 (2/23)
Prior null responders	53 (9/17)	45 (15/33)	19 (3/16)
Outcome for all subjects without SVR24			
On-treatment virologic failure*			
Prior relapsers	8 (2/26)	6 (3/53)	22 (6/27)
Prior partial responders	22 (5/23)	20 (9/46)	78 (18/23)
Prior null responders	35 (6/17)	36 (12/33)	75 (12/16)
Viral relapse†			

Reference ID: 3829051

Prior relapsers	13 (3/23)	8 (4/49)	47 (9/19)
Prior partial responders	6 (1/17)	8 (3/36)	50 (2/4)
Prior null responders	18 (2/11)	20 (4/20)	25 (1/4)

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 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.

In prior partial responders, SVR24 rates in subjects receiving OLYSIO with Peg-IFN-alfa and RBV were 47% and 77% in subjects with HCV genotype 1a and 1b, respectively, compared to 13% and 7%, respectively, in subjects receiving placebo with Peg-IFN-alfa and RBV. In prior null responders, SVR24 rates in subjects receiving OLYSIO with Peg-IFN-alfa and RBV were 41% and 47% in subjects with HCV genotype 1a and 1b, respectively, compared to 0% and 33%, respectively, in subjects receiving placebo with Peg-IFN-alfa and RBV.

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 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.

Reference ID: 3829051

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).

Table 17 shows the response rates in treatment-naïve, prior relapsers, prior partial responders and null responders.

Table 17: Response Rates 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 all 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.

* 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 18 shows the SVR rates by METAVIR fibrosis scores.

Reference ID: 3829051

Table 18: 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)

Two subjects had HIV virologic failure defined as confirmed HIV-1 RNA ≥ 200 copies/mL after previous < 50 copies/mL; these failures occurred 36 and 48 weeks after end of 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 (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 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 19 shows the response rates in treatment-naïve, prior relapsers, prior partial responders and null responders. Table 20 shows the SVR rates by METAVIR fibrosis scores.

Table 19: Response Rates 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 all subjects without SVR12				
On-treatment failure*	9 (3/35)	9 (2/22)	20 (2/10)	45 (18/40)

Reference ID: 3829051

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.

* 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 20: 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)

14.3 OLYSIO in Combination with Sofosbuvir

Adult Subjects with HCV Genotype 1 Infection

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 (Cohort 1), or treatment-naïve subjects and prior null responders with METAVIR fibrosis score F3-F4 and compensated liver disease (Cohort 2).

The 80 enrolled subjects without advanced hepatic fibrosis in Cohort 1 had a median age of 56 years (range 27 to 70 years; with 8% above 65 years); 61% were male; 71% were White, 29% Black or African American, and 25% were Hispanic; 30% had a BMI greater than or equal to 30 kg/m^2; 98% had HCV RNA levels greater than 800,000 IU/mL; 41% had METAVIR fibrosis score F0 or F1 and 59% had METAVIR fibrosis score F2; 78% had HCV genotype 1a, and the remaining patients had HCV genotype 1b; 39% of the overall population and 50% of the subjects with genotype 1a had the NS3 Q80K polymorphism at baseline; 6% had *IL28B* CC genotype, 70% *IL28B* CT genotype, and 24% *IL28B* TT genotype. All subjects were prior null responders to Peg-IFN-alfa and RBV.

The 87 enrolled subjects with advanced hepatic fibrosis in Cohort 2 had a median age of 58 years (range 28 to 70 years; with 3% above 65 years); 67% were male; 91% were White, 9% Black or African American, and 17% were Hispanic; 44% had a BMI greater than or equal to 30 kg/m^2; 84% had HCV RNA levels greater than 800,000 IU/mL; 53% had METAVIR fibrosis score F3 and 47% had METAVIR fibrosis score F4 (cirrhosis); 78% had HCV genotype 1a, and 22% HCV genotype 1b; 31% of the overall population and 40% of the subjects with genotype 1a had the NS3 Q80K polymorphism at baseline; 21% had *IL28B* CC genotype, 56% *IL28B* CT genotype, and 23% *IL28B* TT genotype.

Reference ID: 3829051

Fifty-four percent of subjects were prior null responders to Peg-IFN-alfa and RBV and 46% were treatment-naïve.

Table 21 shows the response rates by combining prior null responders in Cohort 1 and treatment-naïve subjects and prior null responders in Cohort 2. When treatment arms with and without ribavirin were combined, the overall SVR12 rate was 95% (61/64) in subjects with METAVIR fibrosis score F0-F3 who received 12 weeks treatment of OLYSIO in combination with sofosbuvir with/without RBV when pooling both cohorts. The overall SVR12 rate was 96% (22/23) in subjects with METAVIR fibrosis score F4 who received 24 weeks treatment of OLYSIO in combination with sofosbuvir with/without RBV when pooling both cohorts. Addition of RBV did not increase response rates in comparison with OLYSIO in combination with sofosbuvir alone; and therefore these data are not shown in Table 21.

Table 21: Treatment Response by METAVIR Fibrosis Score in Treatment-Naïve Subjects or Prior Null Responders* with HCV Genotype 1 Infection Receiving 12 or 24 Weeks of OLYSIO with Sofosbuvir (COSMOS Trial; Pooled Data for Cohort 1 and 2)

	OLYSIO + Sofosbuvir 12 weeks % (n/N)	**OLYSIO + Sofosbuvir 24 weeks % (n/N)**
Overall SVR12	93 (26/28)	97 (30/31)
F0-3	95 (20/21)	95 (20/21)
F4	86 (6/7)	100 (10/10)
Viral Relapse†	7 (2/28)	0 (0/30)
F0-3	5 (1/21)	0 (0/20)
F4	14 (1/7)	0 (0/10)

SVR12: sustained virologic response 12 weeks after planned EOT.
* Null Responders to prior Peg-IFN-alfa and RBV 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. No subjects experienced virologic on-treatment failure.

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) or a bottle of 7 capsules (emergency supply; NDC 59676-225-07).

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

- OLYSIO should be used in combination with other antiviral drugs for the treatment of CHC infection, and thus contraindications and warnings for these drugs also apply to their use in OLYSIO combination treatment.

Reference ID: 3829051

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 (5.1), Adverse Reactions (6.2), and Drug Interactions (7.3)]*.

Pregnancy

Advise female patients to use an effective contraceptive method during treatment with OLYSIO. Advise patients to see the patient information for other antiviral drugs used in combination with OLYSIO regarding use in 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 Dosage and Administration (2.5), Warnings and Precautions (5.2), Adverse Reactions (6.2), Use in Specific Populations (8.8) and Clinical Pharmacology (12.3)]*.

Photosensitivity

Advise patients of the risk of photosensitivity reactions related to OLYSIO combination treatment and that these reactions may be severe. Patients should be advised to contact their healthcare provider immediately if they develop a photosensitivity reaction. Patients should not stop OLYSIO due to photosensitivity reactions unless instructed by their healthcare provider *[see Warnings and Precautions (5.4)]*.

Patients should be advised to use sun protection measures (such as a hat, sunglasses, protective clothing, sunscreen) during treatment with OLYSIO. Patients should limit exposure to natural sunlight and avoid artificial sunlight (tanning beds or phototherapy) during treatment with OLYSIO.

Rash

Advise patients of the risk of rash related to OLYSIO combination treatment and that rash may become severe. Patients should be advised to contact their healthcare provider immediately if they develop a rash. Patients should not stop OLYSIO due to rash unless instructed by their healthcare provider *[see Warnings and Precautions (5.5)]*.

Administration

Advise patients that OLYSIO should be used only in combination with other antiviral drugs for the treatment of CHC infection. Advise patients to discontinue OLYSIO if any of the other antiviral drugs used in combination with OLYSIO are permanently discontinued for any reason.

Reference ID: 3829051

Advise patients that the dose of OLYSIO must not be reduced or interrupted, as it may increase the possibility of treatment failure.

If the patient misses a dose of OLYSIO and remembers within 12 hours of the usual dosing time, advise the patient to take the missed dose of OLYSIO with food as soon as possible and then take the next dose of OLYSIO at the regularly scheduled time. If a patient misses a dose of OLYSIO by more than 12 hours after the usual dosing time, advise the patient not to take the missed dose of OLYSIO, but to resume the usual dosing of OLYSIO with food at the regularly scheduled time. Inform the patient that he or she should not take more or less than the prescribed dose of OLYSIO at any one time.

Hepatitis C Virus Transmission

Inform patients that the effect of treatment of hepatitis C infection on transmission is not known, and to take appropriate precautions to prevent transmission of the hepatitis C virus.

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: OLYSIO is used in combination with other antiviral medicines. **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?

- If you are pregnant, or plan to become pregnant, talk with your healthcare provider before taking OLYSIO. It is not known if OLYSIO will harm your unborn baby. **Also read the Medication Guides for peginterferon alfa and ribavirin if your healthcare provider prescribes these medications for you in combination with OLYSIO**.
- Females must use an effective form of birth control during treatment with OLYSIO. Talk with your healthcare provider about birth control methods that you may use during treatment with OLYSIO.

OLYSIO may cause serious side effects, including:

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:
  - fainting or near-fainting
  - dizziness or lightheadedness
  - weakness, extreme tiredness
  - chest pain, shortness of breath
  - confusion or memory problems

OLYSIO may cause severe liver problems in some people.

- 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:
  - tiredness
  - weakness
  - loss of appetite
  - nausea and vomiting
  - yellowing of your skin or eyes
  - 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.

- Use sunscreen, and wear a hat, sunglasses, and protective clothing when you will be exposed to sunlight during treatment with OLYSIO.
- Limit sunlight exposure 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:
  - burning, redness, swelling or blisters on your skin
  - mouth sores or ulcers
  - red or inflamed eyes, like “pink eye” (conjunctivitis)

You should not take OLYSIO alone. OLYSIO should be used together with other medicines to treat chronic hepatitis C infection.

What is OLYSIO?

- OLYSIO is a prescription medicine used with other antiviral medicines to treat chronic (lasting a long time) hepatitis C 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.

Reference ID: 3829051

What should I tell my healthcare provider before taking OLYSIO?

Before taking OLYSIO, tell your healthcare provider if you:

- 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 of East Asian descent
- are breastfeeding. It is not known if OLYSIO passes into your breast milk. You and your healthcare provider should decide if you will take OLYSIO or breastfeed. You should not do both.

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.
- If you miss a dose of OLYSIO and it is more than 12 hours until your next dose, take the missed dose as soon as possible with food. Take the next dose of OLYSIO at your regular time.
- If you miss a dose of OLYSIO and it is less than 12 hours until your next dose, skip the missed dose. Take the next dose of OLYSIO at your regular time.
- 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?

- **See "What is the most important information I should know about OLYSIO?"**

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

- skin rash
- itching
- nausea

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

- tiredness
- headache
- 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

It is not known if treatment with OLYSIO will prevent you from infecting another person with the hepatitis C virus during your treatment. Talk with your healthcare provider about ways to prevent spreading the hepatitis C virus.

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.

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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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised October 2015