

OLYSIO™ (simeprevir) capsules, for oral use

Product Description (please also refer to full prescribing information)

- OLYSIO™ (oh li' see oh)
- OLYSIO™ (simeprevir) is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. OLYSIO is a direct-acting antiviral agent against HCV. Efficacy has been established in combination with peginterferon alfa (PegIFN alfa) and ribavirin (RBV) in HCV genotype 1 infected patients with compensated liver disease (including cirrhosis).¹
 - OLYSIO must not be used as monotherapy.¹
 - OLYSIO efficacy in combination with PegIFN alfa and RBV is influenced by baseline host and viral factors.¹
 - OLYSIO efficacy in combination with PegIFN alfa and RBV is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with HCV genotype 1a without the Q80K polymorphism. 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.¹
 - OLYSIO efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes OLYSIO or other HCV protease inhibitors.¹
- OLYSIO is available as 150-mg oral capsules. The recommended dose is 150 mg taken orally once daily with food. The type of food does not affect exposure to simeprevir. The recommended duration of treatment with OLYSIO is 12 weeks in combination with PegIFN alfa and RBV. All treatment-naïve and prior relapser patients, including those with cirrhosis, should receive an additional 12 weeks of PegIFN alfa and RBV (total treatment duration of 24 weeks). All prior non-responder patients (including partial and null-responders), including those with cirrhosis, should receive an additional 36 weeks of PegIFN alfa and RBV (total treatment duration of 48 weeks).¹

Efficacy in Clinical Studies

- OLYSIO has been studied in treatment-naïve patients (2 phase 3 studies) and in patients who relapsed after or failed prior interferon (IFN)-based therapy (1 phase 3 study and 1 phase 2 study).^{2-3,5-6}

Treatment-Naïve Patients: OLYSIO in Combination with PegIFN and RBV

- In a pooled analysis of 2 phase 3 studies (QUEST-1 and QUEST-2)¹⁻⁴, administration of a 150-mg dose of OLYSIO daily in combination with PegIFN and RBV resulted in a significantly higher rate of sustained virologic response (SVR) at 12 weeks following the end of planned treatment (SVR12) (80%; 419/521) than did administration of placebo (50%; 132/264) with PegIFN and RBV in genotype 1 HCV treatment-naïve patients ($P<0.001$). In patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline, rates of SVR12 were 58% (49/84) for patients who received OLYSIO and 52% (23/44) for patients who received placebo; in patients with genotype 1a virus without the NS3 Q80K polymorphism at baseline, rates of SVR12 were 84% (138/165) for patients who received OLYSIO and 43% (36/83) for patients who received placebo. In patients with genotype 1b virus, rates of SVR12 were 85% (228/267) for patients who received OLYSIO and 53% (70/133) for patients who received placebo. A total of 88% of patients (459/521) who received OLYSIO were eligible to shorten therapy to 24 weeks; of these patients, 88% (405/459) achieved SVR12.¹⁻⁴

Treatment-Experienced Patients Who Relapsed After or Failed Prior Interferon-based Therapy: OLYSIO in Combination with PegIFN and RBV

- In a phase 3 study (PROMISE) in patients who had previously relapsed after IFN-based therapy, administration of a 150-mg dose of OLYSIO daily in combination with PegIFN and RBV resulted in a significantly higher rate of SVR12 (79%; 206/260) than did administration of placebo with PegIFN and RBV (36%; 48/133) in patients with genotype 1 HCV who previously relapsed after IFN-based therapy ($P<0.001$).⁵ In patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline, rates of SVR12 were 47% (14/30) for patients who received OLYSIO and 30% (6/20) for patients who received placebo; in patients with genotype 1a virus without the NS3 Q80K polymorphism at baseline, rates of SVR12 were 78% (62/79) for patients who received OLYSIO and 26% (9/34) for patients who received placebo. In patients with genotype 1b virus, rates of SVR 12 were 86% (128/149) for patients who received OLYSIO and 43% (34/79) for patients who received placebo.¹ A total of 93% of patients (241/260) who received OLYSIO were eligible to shorten therapy to 24 weeks; of these patients, 83% (200/241) achieved SVR12.⁵
- In a phase 2 study (ASPIRE) in patients who had not responded to previous PegIFN and RBV treatment, significantly higher rates of SVR at 24 weeks following the end of planned treatment (SVR24) were seen with OLYSIO 150 mg in combination with PegIFN and RBV (67% [44/66] to 80% [52/65]) than with placebo in combination with PegIFN and RBV (23%; 15/66) when dose durations were pooled in genotype 1 HCV patients who had previously not responded to PegIFN and RBV treatment (all $P<0.001$ vs placebo). Neither the presence nor the absence of the Q80K polymorphism affected SVR24 rates among patients with HCV genotype 1a who received OLYSIO 150 mg. Criteria used to shorten treatment duration were not utilized during the trial.⁶

Genotype 4 Patients: Simeprevir in Combination with PegIFN and RBV in Treatment-naïve and Treatment-experienced Patients (Use Not Approved by the Food and Drug Administration [FDA]):

- In an interim analysis of an ongoing, open-label, single-arm, multicenter, phase 3 study (RESTORE) in patients with HCV genotype 4, the overall rate of SVR12 in patients who were administered a 150-mg dose of simeprevir daily in combination with PegIFN and RBV was 85% (52 of 61 patients). The majority of adverse events seen during the first 12 weeks of treatment were grade 1 or 2.⁷

Co-infection Patients: Simeprevir in Combination with PegIFN and RBV in Treatment-naïve and Treatment-experienced Patients Co-infected with Genotype 1 HCV and Human Immunodeficiency Virus Type 1 (HIV-1) (Non-FDA-Approved Use):

- In a single-arm, open-label, phase 3 study (C212), administration of a 150-mg dose of simeprevir daily in combination with PegIFN and RBV resulted in a high rate of SVR12 (74%; 78/106) in treatment-naïve, prior relapse, prior partial responder, or prior null responder patients co-infected with HIV-1. Baseline characteristics (METAVIR fibrosis score, HCV genotype 1 subtype, presence of Q80K polymorphism, IL28B genotype, and baseline CD4+ count) did not have an impact on SVR12 rates. Simeprevir was well tolerated, with a safety profile similar to that seen in HCV-mono-infected patients.⁸

Interferon-free Therapy: Simeprevir in Combination with Sofosbuvir, with or without RBV, in Genotype 1 Prior Null Responders to Previous PegIFN and RBV Therapy Who Had METAVIR Fibrosis Scores of F0 to F2 and Genotype 1 Treatment-naïve and Prior Null Responders Who Had METAVIR Fibrosis Scores of F3 to F4 (Non-FDA-Approved Use):

- In a planned interim analysis of a phase 2 study (COSMOS), 12 weeks of treatment with simeprevir 150 mg and sofosbuvir 400 mg daily led to SVR12 rates of 96% (26/27) with RBV and 93% (13/14) without RBV in genotype 1 HCV prior null responder patients who had METAVIR scores of F0 to F2. Treatment for 12 weeks with simeprevir 150 mg and sofosbuvir 400 mg daily led to rates of SVR4 of 96% (26/27) with RBV and 100% (14/14) without RBV in genotype 1 HCV prior null responder and treatment-naïve patients who had METAVIR scores of F3 to F4. The combination of simeprevir and sofosbuvir with or without RBV was generally well tolerated; anemia and increases in bilirubin levels were primarily seen in patients who received RBV.⁹

Overall Safety (please also refer to Section 6 of the full prescribing information for more information)

In 3 pooled placebo-controlled trials of patients who were treatment-naïve or who had previously relapsed with PegIFN alfa and RBV therapy^{2-3,5}, adverse reactions (all grades) that occurred with at least 3% higher frequency among patients receiving OLYSIO 150 mg once daily in combination with PegIFN alfa and RBV than in patients receiving placebo in combination with PegIFN alfa and RBV during the first 12 weeks of treatment were rash (including photosensitivity), pruritus, nausea, myalgia, and dyspnea.¹ The most common reported adverse reactions (greater than 20% of patients) in patients receiving the combination of OLYSIO with PegIFN and RBV and occurring with at least 3% higher frequency compared to patients receiving placebo in combination with PegIFN alfa and RBV during the first 12 weeks of treatment were: rash (including photosensitivity), pruritus, and nausea. In pooled phase 3 safety data^{2-3,5}, the majority of adverse reactions reported during 12 weeks of treatment with OLYSIO in combination with PegIFN alfa and RBV were grade 1 to 2 in severity.¹ Grade 3 or 4 adverse reactions were reported in 23% of patients receiving OLYSIO in combination with PegIFN alfa and RBV versus 25% of patients receiving placebo in combination with PegIFN alfa and RBV. Serious adverse reactions were reported in 2% of patients receiving OLYSIO in combination with PegIFN alfa and RBV and in 3% of patients receiving placebo in combination with PegIFN alfa and RBV. Discontinuation of OLYSIO or placebo due to adverse reactions occurred in 2% and 1% of patients receiving OLYSIO with PegIFN alfa and RBV and patients receiving placebo with PegIFN alfa and RBV, respectively.¹

Clinical Value, Place in Therapy, Cost Effectiveness

- In phase 3 studies of treatment-naïve patients and patients who relapsed after prior IFN-based therapy, treatment with OLYSIO in combination with PegIFN and RBV was associated with high rates of SVR and a high proportion of patients who were able to shorten their exposure to PegIFN alfa and RBV from 48 weeks to 24 weeks.^{1-3,5}
- In studies with SVR12 as an endpoint, rates of SVR12 in the OLYSIO treatment group were substantially lower in patients infected with genotype 1a virus with the NS3 Q80K polymorphism at baseline than in patients infected with genotype 1a virus without the Q80K polymorphism.^{1-3,5}
- The place in therapy of OLYSIO is as a one capsule, once-daily oral treatment option to be used for the treatment of CHC infection as a component of a combination antiviral treatment regimen with PegIFN alfa and RBV in patients with HCV genotype 1 infection with compensated liver disease (including cirrhosis). OLYSIO in combination with PegIFN alfa and RBV is included in the HCV guidelines (<http://www.hcvguidelines.org/full-report-view>) published by American Association For The Study Of Liver Disease (AASLD) and Infectious Diseases Society of America (IDSA).

- Based on a compilation of assumptions and references, a 1-year budget impact model calculated the incremental drug-only cost (applying December 11, 2013 wholesale acquisition costs) of adding OLYSIO + PegIFN alfa and RBV to a hypothetical US commercial health plan to be -\$0.001 per member per month; incremental total annual drug-only costs were found to be approximately -\$40 per treated member. When drug costs plus outcomes (SVR) were considered, this resulted in a health plan's total annual cost per SVR decrease of \$2,844.

Summary

OLYSIO is a one capsule, once-daily option indicated for the treatment of CHC infection as a component of a combination antiviral treatment regimen.¹ Efficacy has been established in combination with PegIFN alfa and RBV in HCV genotype 1 infected patients with compensated liver disease (including cirrhosis). OLYSIO in combination with PegIFN alfa and RBV was associated with high rates of SVR relative to placebo in combination with PegIFN alfa and RBV.^{1-3,5-6} In phase 3 studies, in the OLYSIO treatment group, rates of SVR12 were substantially lower in patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to patients infected with genotype 1a virus without the Q80K polymorphism.^{1-3,5} The most common reported adverse reactions (greater than 20% of patients) in patients receiving the combination of OLYSIO with PegIFN and RBV and occurring with at least 3% higher frequency compared to patients receiving placebo in combination with PegIFN alfa and RBV during the first 12 weeks of treatment were: rash (including photosensitivity), pruritus, and nausea.¹ Adverse reactions (all grades) that occurred with at least 3% higher frequency among patients receiving OLYSIO 150 mg once daily in combination with PegIFN alfa and RBV compared to patients receiving placebo in combination with PegIFN alfa and RBV during the first 12 weeks of treatment in pooled phase 3 trials^{2-3,5} were rash (including photosensitivity), pruritus, nausea, myalgia, and dyspnea.¹

References

1. OLYSIO™ (simeprevir) Capsules [prescribing information]. Titusville, NJ: Janssen Therapeutics, Division of Janssen Products, LP.
2. Jacobson I, Dore GJ, Foster GR, et al. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection in treatment-naïve patients: results from QUEST-1, a phase III trial. Poster presented at: Digestive Disease Week (DDW); May 18-21, 2013; Orlando, FL. Poster 1674582.
3. Poordad F, Manns M, Marcellin P, et al. Simeprevir with peginterferon-α2a or -α2b and ribavirin in treatment-naïve HCV genotype-1 patients: QUEST-2, a randomized phase III trial. Data presented at Digestive Disease Week (DDW); May 18-21, 2013; Orlando, FL.
4. Jacobson IM, Dore GJ, Foster GR, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype 1 infection in treatment-naïve patients: efficacy in difficult-to-treat patient sub-populations in the QUEST-1 and 2 phase III trials. Poster presented at: Liver Meeting®, the 64th Annual Meeting of the American Association for the Study of Liver Disease; November 1-5, 2013; Washington, DC. Poster 1122.
5. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. *Gastroenterology*. 2014;doi:10.1053/j.gastro.2014.02.051.
6. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology*. 2014 Feb;146(2):430-441.
7. Moreno C, Hezode C, Marcellin P, et al. Simeprevir with peginterferon/ribavirin in treatment-naïve or experienced patients with chronic HCV genotype 4 infection: interim results of a phase III trial. Poster and presentation at: HEP DART 2013; December 8-12, 2013; Big Island, Hawaii.
8. Dieterich D, Rockstroh J, Orkin C, et al. Simeprevir plus pegIFN/ribavirin in HCV genotype-1/HIV-1 co-infection (Study C212). Oral presentation presented at the Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2014; Boston, MA.
9. Jacobson IM, Ghalib R, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (SMV, TMC435) plus sofosbuvir (SOF, GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: the COSMOS study. Oral presentation presented at the 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); November 1-5, 2013; Washington, DC.