Brand Name: Olysio ®
Generic Name: Simeprevir
Manufacturer: Janssen Therapeutics
Drug Class: NSIII/IVA protease inhibitor
Uses

- **Labeled**: hepatitis C infection (genotype I)
- **Unlabeled:** hepatitis C infection (genotype IV)

Mechanism of Action[1, 2, 3, 4]
Simeprevir blocks the protease HCV NS3/4A, which prevents the replication of the hepatitis C virus. HCV NS3/4A protease functions as an enzyme that is responsible for the conversion of polyproteins to mature viral proteins

Pharmacokinetics[1, 2, 3, 4]

T_{max}	4 – 6 hours
V_D	Not yet determined in studies
$t_{1/2}$	10 – 13 hours in healthy patients 41 hours in subjects with HCV infection
Protein binding	99.9%, primarily albumin
Bioavailability (F)	Orally bioavailable (no value reported by manufacturer)

Metabolism [1, 2, 3, 4]
Simeprevir is primarily metabolized through the liver via CYP3A4. Simeprevir inhibits intestinal CYP1A2 and 3A4, but not hepatic CYPs. Metabolites are inactive and excreted primarily through the biliary tract. 91% is eliminated fecally (31% unchanged), and less than 1% is recovered in the urine.

Efficacy [5, 6, 7]
Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2014; 384: 403 – 13

- Study design:
  Multicenter, double-blind, randomized, placebo-controlled phase III trial carried out to determine the safety and efficacy of simeprevir in combination with currently approved treatments.
- Description:
  Methods
  Treatment naïve patients with hepatitis C (HCV) genotype I were assigned to one of two groups in a parallel study format: either simeprevir in combination with ribavirin and peginterferon alfa or placebo in combination with ribavirin and peginterferon alfa. Included patients were eighteen years of age or older, had chronic HCV genotype I

infection, a plasma HCV RNA load of greater than 10,000 IU/mL, and had no prior treatments for their infection. Patients were excluded if they had decompensated liver disease, a non-HCV related liver disorder, HIV infection, hepatitis B (HBV), any other HCV genotype aside from type I, significant laboratory abnormalities, any active disease, and were pregnant or planning to conceive.

Patients in the treatment group (n=264) received simeprevir 150mg daily with ribavirin and peginterferon alfa for 12 weeks, followed by either 12 or 36 weeks of placebo, peginterferon alfa, and ribavirin. Duration of therapy was based on HCV RNA levels. Patients in the control group (n=130) received placebo with peginterferon and ribavirin (in the same dosing scheme as the treatment group) for 12 weeks, followed by peginterferon alfa and ribavirin for 36 weeks.

Results:

The primary endpoint of the study was to determine the number of patients that achieved HCV RNA concentrations of less than 25 IU/mL undetectable or less than 25 IU/mL detectable or undetectable at 12 weeks following the end of treatment (SVR12). SVR12 was reached in 80% of patients treated with simeprevir versus 50% of the control group (mean difference of 29.3 %; 95% CI 20.1 – 38.6; $p < 0.0001$).

Many secondary endpoints were found in the study. Comparison of sustained virologic response 24 weeks after the end of treatment (SVR24) favored simeprevir 83% versus 60% in the placebo arm (weighted difference 18.1%; 95% CI -0.4 – 36.6, $p = 0.0253$). 85% of simeprevir patients met criteria for response-guided therapy to complete treatment at week 24. Rapid virologic response (RVR) at week 4 was 80% in the simeprevir group versus 12% in the placebo group (68% difference; 95% CI 60.5 - 75.4). Incidence of treatment failure and viral relapse favored simeprevir: 9% versus 34% (difference of -24.9%; 95% CI -33.7 to -16) and 9% versus 21% in the placebo group (mean difference -12.5; 95% CI -22.1 to – 3.0), respectively. Overall frequencies of adverse events were similar amongst the two groups at 12 weeks of therapy and by the conclusion of treatment. Impairment in productivity and increase in fatigue worsened by similar amounts in both groups from baseline as assessed by patient-reported statistics.

- Limitations:

  The study was designed, analyzed, interpreted, and reviewed by the company producing simeprevir. Incidence of side effects in the simeprevir group may have been precipitated by either ribavirin or peginterferon alfa. Most patients completing the trial did not have cirrhosis, a common complication in hepatitis, thereby limiting the applicability to such patients. With a number of new HCV medications being released, standards of therapy are being changed frequently. As a result of the study design, no efficacy claims may be made against other protease inhibitors (e.g. telaprevir or boceprevir), which represented the previous standard of care.

- Conclusion:

  Patients treated with simeprevir, ribavirin, and peginterferon alfa has significantly higher sustain virologic responses at both 12 and 24 weeks following therapy relative to placebo, ribavirin, and peginterferon alfa. Furthermore, simeprevir produced better suppression of HCV viral loads in a shorter period of time than placebo, peginterferon alfa, and

ribavirin. Treatment failure was far less common with simeprevir therapy, and adverse effects were comparable to the control group. Simeprevir represents a new treatment for HCV genotype I infections with greater efficacy than placebo in treatment naïve patients.

Forns X, Lawitz, Zeusem S, Gane E, Bronowicki JP, Andreone P, 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; 146: 1669 – 79

- Study Design:
  Multicenter, randomized, double-blind, placebo-controlled, phase III trial
- Description:
  Methods:
  Patients were included in the study if they were 18 years of age or older, had HCV genotype I infection, HCV RNA levels greater than 10,000 IU/mL, and had relapsed after 24 weeks of more of interferon based therapy or within two months after the end of treatment. A biopsy of the liver within three years of enrollment was required to show hepatic damage consistent with HCV infection. Patients were excluded from the trial if they had hepatic decompensation, non – HCV related liver disease, HIV infection, non-genotype I HCV infection, marked laboratory abnormalities, any other active disease, were pregnant, or planning pregnancy.
  Included patients were stratified based on HCV 1 subtype (Ia, Ib, etc) in a 2:1 ratio into two groups. The treatment group (n=260) received 150mg simeprevir daily with peginterferon α - 2a weekly and daily ribavirin (PR) for 12 weeks followed by response guided therapy (RGT) with PR for 12 or 36 weeks. The control group (n=133) received placebo with PR for 12 weeks followed by PR alone for 36 weeks. Patients in both the treatment and control groups were followed until 72 weeks following initiation of the trial.
  Results:
  The primary endpoint of the study was the proportion of patients whom achieved sustained virologic response (SVR) 12 weeks following the end of treatment. The results favored simeprevir 79.2% versus 36.1% (43.8% difference; 95% CI, 34.6 – 53; $p < 0.001$).
  Multiple secondary endpoints were reported. Sustained virologic response at 24 weeks after the end of therapy (SVR24) favored simeprevir 78.3% versus 31.3% (difference 47.1%; 95% CI, 34.8-59.5; $p <0.001$). Rapid virologic response (RVR) rate favored simeprevir 77.2% versus 3.1%. 92.7% of patients treated with simeprevir that met RGT criteria to complete treatment at week 24. On-treatment failure favored simeprevir 3.1% versus 27.1% in the placebo arm. The most frequent adverse events (> 25% of patients) in the simeprevir group were headache, fatigue, and influenza-like illness. Incidence of rash, pruritus, neutropenia, and anemia was comparable to the placebo group.
- Limitations:
  94.4% of the enrollees were white. Considering the prevalence of hepatitis C in Latino and African-American populations, the results of this study may be limited in such populations. With therapy for the treatment of hepatitis C changing rapidly, it is difficult

to find a comparator on which therapy may be based. Studies directly involving other protease inhibitors should be performed before relative efficacy is established.

- Conclusion:
  It can be clearly stated that simeprevir in combination with peginterferon alfa and ribavirin represents superior therapy to placebo with peginterferon and ribavirin, as the treatment group showed more benefit in eliciting a sustained virologic response at weeks 12 and 24, showed lower rates of treatment failure, and had a pronounced effect via rapid virologic response. Adverse effects mimic what has been found in other studies and do not differ significantly than that of placebo with peginterferon alfa and ribavirin.

Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet.* Published online July 28, 2014.

- Study Design:
  Randomized, open-label trial of 168 patients comparing the efficacy of simeprevir and sofosbuvir with or without ribavirin
- Description:
  Methods:
  Included patients were 18 years of age or older, had chronic HCV genotype I, HCV titers > 10000 IU/mL, had compensated liver disease, and had estimated glomerular filtration rates of greater than or equal to 60 mL/min per 1.73m^2. Patients were excluded if they had HIV infection. After appropriately including patients, two cohorts were formed: patients who previously did not respond to therapy with peginterferon alfa and ribavirin and had absent to moderate liver fibrosis (METAVIR score F0-F2) and patients who previously did not respond to peginterferon alfa and ribavirin OR be treatment naïve and have severe liver fibrosis (METAVIR score F3-F4). Patients were then randomized in a 2:2:1:1 fashion into the following groups: simeprevir and sofosbuvir with ribavirin for 24 weeks (cohort I, group I), simeprevir and sofosbuvir without ribavirin for 24 weeks (cohort I, group II), simeprevir and sofosbuvir with ribavirin for 12 weeks (cohort II, group I), and simeprevir and sofosbuvir without ribavirin for 12 weeks (cohort II, group II). Patients were followed for a total of 48 weeks, including end of therapy assessments, in both groups. Assessments during treatment included laboratory evaluation, vital signs, electrocardiography, and incidence and severity of adverse events.
  Results:
  The primary endpoint of the study was whether a sustained virologic response was ascertained at 12 weeks after the end of therapy (SVR12). 92% of patients in the intent to treat population achieved SVR12 (95% CI 81-96) in cohort I, and 94% in cohort II (no CI reported). 91% of patients receiving ribavirin in both cohorts versus 95% of patients who did not receive ribavirin achieved SVR12
  The trial had two secondary endpoints. All patients who achieved SVR12 (91% overall) also achieved a sustained virologic response at 4 weeks following end of therapy. Rapid

virologic response (RVR), was achieved in 81% of patients overall. No patients experienced on-treatment virologic failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. Four patients discontinued all treatment because of adverse events. The most common adverse events were fatigue (31%), headache (20%), and nausea (16%), which appears consistent with past studies. Rash, pruritus, hyperbilirubinemia, and anemia developed more frequently in patients receiving ribavirin than those not receiving ribavirin. The most common laboratory value abnormalities reported were hyperglycemia, hyperbilirubinemia, and amylase.

- Limitations:
  A power calculation was not performed before the study began, and it should also be noted that the target number of patients was not reached in cohort I to achieve the desired 95% CI range. As a result, the investigators allowed treatment naïve patients and nonresponders into cohort II, thereby skewing some of their data to potentially favor cohort II. The trial was open label in nature. While objective data was required to fulfill the final outcome (HCV RNA titers), it cannot be discounted that bias could have been present on behalf of the researchers or the patients. The funding source of the study, Janssen Pharmaceuticals, was responsible for the study design, data collection, data analysis, data interpretation, and helped write the article. Despite not being listed as part of the study's exclusion criteria, the investigators excluded patients whom had previously failed protease inhibitor therapy or had protease-inhibitor-related mutations.
- Conclusion:
  Patients previously failing interferon - based therapy receiving simeprevir and sofosbuvir for HCV genotype I had a high rate of sustained virologic response at 12 weeks following the end of therapy. Treatment for 24 weeks and the addition of ribavirin did not definitively improve rates of sustained virologic response versus patients treated for 12 weeks without ribavirin. Current guidelines recommend treatment with sofosbuvir and simeprevir for patients who failed prior therapies or those with an inherent intolerance to interferon.

Contraindications[1, 2, 3, 4]

- Pregnancy:
  Simeprevir carries a category C pregnancy rating. However, simeprevir should not be used as monotherapy, and the recommend combination of simeprevir with ribavirin/peginterferon alfa carries a pregnancy category X rating.
- Men whose female partners are pregnant:
  Simeprevir does not cause male-mediated teratogenicity as monotherapy. The regimen of simeprevir + ribavirin/peginterferon alfa has been shown to cause birth defects, and should not be used in males whose females partners are pregnant.

Precautions[1, 2, 3, 4]

- Photosensitivity reactions:

May present similar to a sunburn (sensitivity, burning, painful, blistering), with affected areas having been exposed to light. Consider discontinuation of therapy is reaction occurs. Reactions occur most frequently within four weeks of initiation of therapy.

- Rash:
  May present as moderate to severe in sensitivity. Consider discontinuation of therapy. Usually presents within four weeks of initiation of therapy.
- Patients with sulfonamide hypersensitivity:
  Simeprevir contains a sulfa moiety. Definitive data regarding exact reaction in patients with sulfa allergy is lacking.
- Asian ethnicity:
  Asian patients have a higher exposure to simeprevir relative to the general population, and thus have a higher rate of adverse reactions. No dose adjustment recommendations are available for this population.
- Use as monotherapy:
  Current data limits the use of simeprevir as a single entity for treatment of hepatitis C. Simeprevir should be combined with peginterferon alfa and ribavirin during treatment.
- Concomitant use with CYP3A inducers or inhibitors:
  Medications that alter the metabolism of simeprevir should be used with caution to prevent subtherapeutic or supratherapeutic drug levels. See below for a detailed list of drug interactions.

Adverse effects[1, 2, 3, 4]

- Rash (28%)
- Pruritus (22%)
- Nausea (22%)
- Hyperbilirubinemia
  - Grade I: 27%
  - Grade II: 18%
  - Grade III: 4%
- Myalgia (16%)
- Dyspnea (12%)
- Photosensitivity (5%)

Drug Interactions [1, 2, 3, 4, 8]

- CYP3A4 inhibitors:
  Simeprevir is metabolized hepatically by CYP3A4 enzymes. Concomitant use of CYP3A4 inhibitors may increase simeprevir exposure within the body, potentially leading to toxicities or increased rates of adverse reactions. Select drugs that inhibit CYP3A4 include: tacrolimus, sirolimus, cyclosporine, clarithromycin, erythromycin, darunavir, ritonavir, midazolam, ketoconazole, itraconazole, posaconazole, fluconazole, voriconazole, milk thistle, grapefruit juice, ciprofloxacin, imatinib, aprepitant, cimetidine, fluvoxamine, and others.
- CYP3A4 inducers:

Simeprevir is metabolized hepatically by CYP3A4 enzymes. Concomitant use of CYP3A4 inducers may decrease simeprevir exposure within the body, potentially leading to therapeutic failure at the conclusion of scheduled treatment. Select drugs that induce CYP3A4 include: rifampin, efavirenz, St. John's wort, cobicistat, phenytoin, phenobarbital, barbiturates, dexamethasone, pioglitazone, and others.

- Digoxin:
  Simeprevir inhibits p-glycoprotein, which may result in increased therapeutic concentrations of digoxin.
- Antiarrhythmics (disopyramide, flecainide, mexiletine, propafenone, quinidine, amiodarone):
  Intestinal inhibition of CYP3A4 by simeprevir may result in increases of antiarrhythmic drug levels
- Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin):
  The listed anticonvulsants may significantly decrease simeprevir levels secondary to their induction of CYP3A4.
- Calcium channel blockers (amlodipine and other dihydropyridines, diltiazem, and verapamil):
  Simeprevir mediated inhibition of intestinal CYP3A4 and p-glycoprotein may result in increased levels of calcium channel blockers.
- Protease inhibitors (atazanavir, lopinavir, tipranavir, etc.):
  It is not recommended to administer any protease inhibitor with simeprevir due to CYP3A4 inhibition or induction, leading to variable levels of simeprevir.
- 5-HMG CoA Reductase Inhibitors (rosuvastatin, atorvastatin, simvastatin):
  Concomitant administration of simeprevir with select statins may increase their therapeutic levels due to intestinal inhibition of either CYP3A4 or OATP1B1.
- PDE – 5 inhibitors (sildenafil, tadalafil, vardenafil):
  Concomitant administration of simeprevir with erectile dysfunction medications may increase their therapeutic levels due to intestinal inhibition of either CYP3A4 or OATP1B1.
- Ethanol:
  Ethanol induces CYP3A4, which may lead to reduced plasma concentrations of simeprevir.

Dosing and administration[1, 2, 3, 4]

- How supplied: OLYSIO ® 150mg capsules
- Adult dosage: 150mg by mouth daily + ribavirin and peginterferon alfa
- Geriatric Dose: 150mg by mouth daily + ribavirin and peginterferon alfa
- Pediatric dose: safety and efficacy data has not been established
- Renal impairment
  - No dosing changes are required in patients with renal dysfunction. However, simeprevir has not been studied in end stage renal disease.
- Dialysis: unlikely to significantly remove simeprevir
- Hepatic impairment

    - Child-Pugh Class A
        - No dose adjustments necessary
    - Child-Pugh Class B and C
        - No specific dose recommendations available. However, simeprevir is hepatically metabolized and patients with such hepatic dysfunction have been shown to have higher therapeutic levels of simeprevir. Administration of simeprevir with this population should be cautioned.
- Special populations
    - Pregnancy: simeprevir is not recommended due to category X status of medications combined with simeprevir
    - Breast feeding: it is unknown if simeprevir is released in to breast milk. Its use in such patients is not recommended unless the benefits outweigh the risks.
    - East Asian ancestry: no specific dosage recommendations are available

Patient Education

- Warn female patients about use of simeprevir in combination with peginterferon alfa and ribavirin during pregnancy. Male patients should avoid intercourse during therapy and for six months following last dose to prevent pregnancy.
- Take simeprevir with food to increase absorption and maximize bioavailability
- Missed doses should be taken as soon as they are remembered. If it is within twelve hours of the following dose, the missed dose should be skipped and no additional simeprevir should be taken to account for the missed dose.
- Common side effects attributable to simeprevir include pruritus, myalgia, and nausea.
- If other medications in your regimen are discontinued (e.g. peginterferon alfa and ribavirin), the simeprevir should also be discontinued. Simeprevir should never be given by itself for the treatment of hepatitis C.

Conclusion [2, 3]

Olysio ® (simeprevir) is a novel protease inhibitor for the treatment of hepatitis C. Safety and efficacy studies have shown simeprevir-containing regimens to be superior to treatment to such regimens without simeprevir. Furthermore, simeprevir carries a similar adverse effect profile to other protease inhibitors in its class, but has the advantage of once daily dosing. Presently, the treatment of hepatitis C is consistently changing due to the introduction of agents such as simeprevir, sofosbuvir, and others on to the market. Although simeprevir represents a distinct advantage over the past standard of care, further trials are needed to compare the relative safety and efficacy of all newly introduced agents. Practitioners should regularly review the changing hepatitis C guidelines to ensure their patients are receiving the safest and most efficacious treatment.

References:

1. Simeprevir Overview. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2014.
   Available at: http://www.clinicalpharmacology.com. Accessed: September 22, 2014
2. Simeprevir. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson
   Micromedex. Updated periodically. Accessed September 22, 2014.
3. Simeprevir [package insert]. Janssen Therapeutics: Titusville, NJ; 2013
4. Simeprevir. Lexi-Comp (Lexi-Drugs) [computer program]. Lexi-Comp, Inc; September 29, 2014.
5. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2014; 384: 403 – 13
6. Forns X, Lawitz, Zeusem S, Gane E, Bronowicki JP, Andreone P, 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; 146: 1669 – 79
7. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet.* Published online July 28, 2014.
8. Indiana University Division of Clinical Pharmacology. P450 Drug Interaction Table [updated July 12, 2013]. Indiana University Department of Medicine. Available at http://medicine.iupui.edu/clinpharm/ddis/main-table/. Accessed September 29, 2014

Prepared by: Galen M. Kabulski, Doctor of Pharmacy Candidate