

Simeprevir (*Olysio*)

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Drug Summary

Simeprevir has provided an excellent alternative to the older first-generation NS3/4A protease inhibitors (boceprevir and telaprevir) for the treatment of patients with genotype 1 HCV. Simeprevir is convenient (once-daily dosing), well-tolerated, and has less extensive drug-drug interactions than the first-generation protease inhibitors. The combination of simeprevir plus peginterferon plus ribavirin for genotype 1 is no longer a recommended or alternative regimen, primarily because of the toxicity and long duration of treatment associated with the use of peginterferon and ribavirin. In contrast, the combination of simeprevir and sofosbuvir, with or without ribavirin in patients with genotype 1 has been very well tolerated and has generated overall SVR12 rates greater than 90%. The cost of simeprevir when used for a 12 week course of therapy is approximately \$66,000 and the combination of simeprevir plus sofosbuvir for 12 weeks (\$150,000) is significantly more expensive than a 12-week course with either ledipasvir-sofosbuvir or ombitasvir-paritaprevir-ritonavir and dasabuvir. Based on a subanalysis of a relatively small number of patients in the COSMOS trial, the FDA recommends extending the duration of therapy to 24 weeks, which is extremely expensive. Simeprevir, with or without ribavirin, is under study in combination with other agents, including the NS5A inhibitor samatasvir, the NS5A inhibitor daclatasvir, and the non-nucleoside NS5B inhibitor TMC647055 (given with the pharmacologic booster ritonavir), as all-oral therapy.

Class and Mechanism

Simeprevir (*Olysio*) is a NS3/4A hepatitis C virus (HCV) protease inhibitor. Simeprevir is a macrocyclic compound that non-covalently binds to and inhibits the NS3/4A HCV protease, a protein that is responsible for cleaving and processing the HCV-encoded polyprotein, a critical step in HCV viral life cycle. Simeprevir is considered a second generation HCV protease inhibitor because of the enhanced binding affinity and specificity to NS3/4A when compared with the first-generation protease inhibitors with linear structure.

Manufacturer for United States

Simeprevir (*Olysio*) ([Figure 1](#)) is manufactured by Janssen Research & Development. Simeprevir was jointly developed by Janssen Research & Development and Medivir AB, originally known as compound TMC-435. Janssen has a collaborative agreement with Idenix Pharmaceuticals for the clinical development of combination oral direct acting therapies for the treatment of hepatitis C infection and simeprevir is among the drugs included in this agreement.

Cost and Medication Access

The wholesale acquisition cost (WAC) for simeprevir is \$790 per 150 mg capsule. The cost for a 28-days supply of simeprevir is \$22,120 and a 12-week supply is \$66,360. Thus, a typical 12-week treatment course of simeprevir when used with a total of 24-weeks of peginterferon plus ribavirin will cost approximately \$85,000. A 12-week course of simeprevir plus sofosbuvir costs approximately \$150,000. Janssen has a simeprevir patient assistance program for treatment eligible patients with hepatitis C who are not able to obtain access to simeprevir. Medical providers and patients can learn more about this program by visiting the [Janssen Prescription Assistance Program](#) website or by calling 1-855-565-9746.

Adverse Effects

The most common adverse effects attributable to simeprevir are rash (including a potentially serious photosensitivity reaction), pruritus, and nausea.

- The photosensitivity reaction that can occur with simeprevir most often has an onset during the first 4 weeks of therapy, but can develop at any time on treatment ([Figure 3](#)).
 - Patients taking simeprevir should limit sun exposure, use protective sun exposure measures, and avoid use of any tanning device.
 - If a photosensitivity rash does occur while taking simeprevir, discontinuation of simeprevir should be considered and the patient should have close monitoring until the rash has resolved.
 - Rash not related to photosensitivity can also occur and similar to the photosensitivity rash most often develops during the first 4 weeks of therapy.
 - Simeprevir contains a sulfonamide moiety, but insufficient data exist to know the risk of taking simeprevir in persons with a prior "sulfa allergy".
 - Patients taking simeprevir may experience transient and increases in serum bilirubin levels that peak at week 2 of treatment that are typically mild in severity and not associated with elevated hepatic aminotransferase levels.
 - Simeprevir is pregnancy category C.
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Key Drug Interactions

Simeprevir is primarily metabolized via CYP3A enzymes and thus administering simeprevir with medications that have moderate or strong induction of CYP3A may significantly reduce levels of simeprevir (examples include rifampin, St. John's wort, and most anticonvulsants). In contrast,

medications that have moderate or strong inhibition of CYP3A may significantly increase levels of simeprevir, including clarithromycin, ketoconazole, ritonavir, and *Silybum marianum* (milk thistle). Accordingly, simeprevir should not be given with moderate or strong inducers or inhibitor of CYP3A. Simeprevir is an inhibitor of CYP1A2 and intestinal CYP3A, but not hepatic CYP3A4. Levels of medications that undergo primary metabolism via CYP3A4 may increase if coadministered with simeprevir. In addition, simeprevir has complex drug-drug interactions with many HIV antiretroviral medications and use of simeprevir is not recommended with cobicistat-containing products, efavirenz, etravirine, delavirdine, nevirapine, or any HIV protease inhibitor (ritonavir-boosted or unboosted). See the [Simeprevir \(Olysio\) Full Prescribing Information](#) for a detailed description of drug interactions with simeprevir.

For complete information on simeprevir-related drug interactions, see the [Drug Interactions section in the Simeprevir \(Olysio\) Prescribing Information](#).

Figures

Figure 1 Bottle - Simeprevir (*Olysio*)

Photo: Andrew Karpenko, University of Washington



Figure 2 Capsules - Simeprevir (*Olysio*)

Photo: Andrew Karpenko, University of Washington



Figure 3 Simeprevir Rash

Pruritic rash on hands of patient that started 2 weeks into treatment with simeprevir plus sofosbuvir. The photograph is taken 10 weeks into treatment. The rash only manifested in sun exposed areas.

This photograph is courtesy of Dr. John D. Scott, MD.



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PDF created December 15, 2018, 10:43 am

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