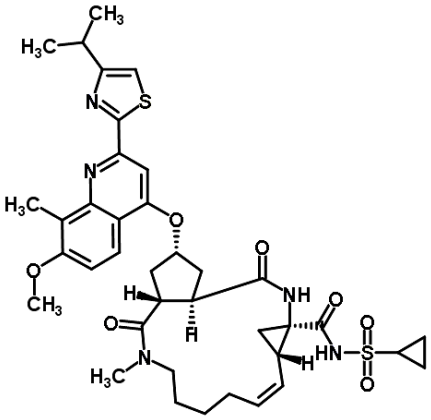
Simeprevir PK Fact Sheet

Details

Generic Name	Simeprevir
Trade Name	Olysio®
Class	NS3/4A protease inhibitor
Molecular Weight	749.94
Structure	

Summary of Key Pharmacokinetic Parameters

Linearity/non-linearity	Plasma Cmax and AUC increased more than dose proportional after multiple doses between 75 mg and 200 mg once daily, with accumulation occurring following repeated dosing.
Steady State	Steady-state was reached after 7 days of once daily dosing.
Plasma Half life	41 h (200 mg once daily, multiple dose in HCV infected patients) [*cf* 10-13 h in HCV-uninfected subjects]
Cmax	Not determined
Cmin	1936 ± 2640 ng/ml (mean ± sd, HCV subjects)
AUC	57,469 ± 63571 ng.h/ml (mean ± sd, HCV subjects) (Pooled population PK estimates of exposure after 150 mg once daily for 12 weeks in genotype 1 patients: White 55,619 ng.h/ml; Black 47,986 ng.h/ml; Asian 196,750 ng.h/ml)[1]. Simeprevir AUC was about 2- to 3-fold higher in HCV infected patients compared to that observed in healthy subjects.
Interindividual Variation	87% for AUC_{0-24} in Phase I study [1]
Bioavailability	62%
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 (928 kcal) and 69% after a normal caloric (533 kcal) breakfast, and delayed the absorption by 1 hour and 1.5 hours, respectively.
Protein Binding	>99.9%
Volume of Distribution	Not determined
CSF:Plasma ratio	Not determined
Semen:Plasma ratio	Not determined
Renal Clearance	Renal clearance plays an insignificant role in the elimination of simeprevir Less than 1% of the administered dose was recovered in urine.

Renal Impairment	Renal elimination of simeprevir is negligible and it is not expected that renal impairment will have a clinically relevant effect on simeprevir exposure. No dose adjustment of simeprevir is required in patients with mild or moderate renal impairment. Compared to healthy subjects with normal renal function (eGFR ≥ 80 ml/min), the mean steady-state AUC of simeprevir was 62% higher in subjects with severe renal impairment (eGFR below 30 ml/min). As exposure may be increased in HCV infected patients with severe renal impairment, caution is recommended when prescribing simeprevir to these patients.
Hepatic Impairment	Plasma exposure of simeprevir in HCV infected patients was about 2- to 3-fold higher compared to that observed in healthy subjects. Compared to healthy subjects with normal hepatic function, the mean steady-state AUC of simeprevir was 2.4-fold higher in non-HCV infected subjects with moderate hepatic impairment (Child-Pugh class B) and 5.2-fold higher in non-HCV infected subjects with severe hepatic impairment (Child-Pugh class C). No dose adjustment of simeprevir is necessary in patients with mild or moderate hepatic impairment; no dose recommendation can be given for patients with severe hepatic impairment (Child-Pugh class C). The safety and efficacy of simeprevir have not been studied in HCV infected patients with moderate or severe hepatic impairment (Child-Pugh class B or C), therefore particular caution is recommended in these patients.

Metabolism and Distribution

Metabolised by	CYP3A4 (involvement of CYP2C8 and CYP2C19 cannot be excluded).
Inducer of	Does not induce CYP1A2 or CYP3A4 in vitro.
Inhibitor of	Intestinal CYP3A (mild), CYP1A2 (mild), P-gp, OATP1B1, MRP2 [1,2] No effect on hepatic CYP3A, CYP2C9, CYP2C19, CYP2D6, UGT1A1 [1,2] Inhibits the uptake transporters OATP1B1 and NTCP and the efflux transporters P-gp/MDR1, MRP2 and BSEP. (The in vitro inhibitory profile of simeprevir for human BCRP, OATP1B3 and OCT2 has not been studied.)
Transported by	P-gp, MRP2, OATP1B1, OATP2B1, OATP1B3.

References

Unless otherwise stated (see below), information is from:
Olysio® Summary of Product Characteristics, Janssen-Cilag *(discontinued).*
Olysio® US Prescribing Information, Janssen.

1. FDA Antiviral Drugs Advisory Committee Meeting Briefing Document: Simeprevir. October 2013
2. Sekar V *et al*. 2010, *J Hepatol*, 52(S1): S416 (Abstract 1076).