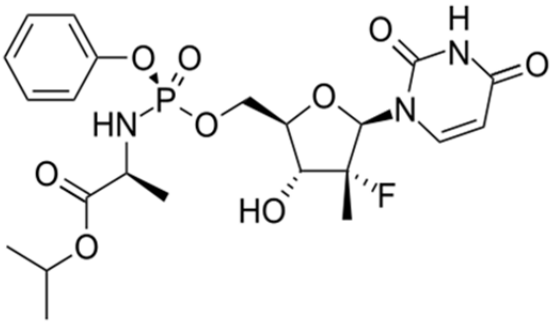
Sofosbuvir PK Fact Sheet

Details

Generic Name	Sofosbuvir (SOF)
Trade Name	Sovaldi®
Class	NS5B nucleotide polymerase inhibitor
Molecular Weight	529.45
Structure	

Summary of Key Pharmacokinetic Parameters

Following oral administration of sofosbuvir, the majority (>90%) of systemic drug exposure is as GS-331007, which is phosphorylated to the active triphosphate catabolite. GS-331007 is considered the primary analyte of interest for purposes of PK analyses.

Linearity/non-linearity	Sofosbuvir and GS-331007 AUCs are near dose proportional over the dose range of 200-1200 mg.
Plasma Half life	0.4 h (sofosbuvir); 27 h (GS-331007)
Cmax	603 (47) ng/ml (sofosbuvir); 1378 (19) ng/ml (GS-331007) [1] [Data are mean (CV%) obtained with sofosbuvir 400 mg once daily in HCV-infected subjects (n=8) from the control arm of the hepatic impairment study.]
Cmin	Cmin of sofosbuvir or GS-331007 is not a key PK parameter for either safety or efficacy.
AUC	1010 ng.h/ml (sofosbuvir); 7200 ng.h/ml (GS-331007) [Based on population pharmacokinetic analysis in subjects with genotypes 1 to 6 HCV infection (n=986)]. 828 ng.h/ml (sofosbuvir); 6790 ng.h/ml (GS-331007) [Geometric mean based on population pharmacokinetic analysis in subjects with genotypes 1 to 6 HCV infection (n=1695)].
Interindividual Variation	Not determined
Bioavailability	Not determined
Absorption	Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardised high fat meal slowed the rate of absorption of sofosbuvir. The extent of absorption of sofosbuvir was increased approximately 1.8-fold, with little effect on peak concentration. The exposure to GS-331007 was not altered in the presence of a high-fat meal.
Protein Binding	61-65% (sofosbuvir); protein binding of GS-331007 is minimal.
Volume of Distribution	Not determined
CSF:Plasma ratio	Not determined
Semen:Plasma ratio	Not determined
Renal Clearance	~80% excreted in the urine (78% as GS-331007, 3.5% as sofosbuvir)
Renal Impairment	No dose adjustment of sofosbuvir is required for patients with mild or moderate renal impairment. The safety and appropriate dose of sofosbuvir have not been established in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis.
Hepatic Impairment	No dose adjustment of sofosbuvir is warranted in mild, moderate or severe hepatic impairment. The safety and efficacy of sofosbuvir have not been established in patients with decompensated cirrhosis.

Metabolism and Distribution

Metabolised by	No evidence of CYP450 or UGT mediated metabolism of sofosbuvir or GS-331007. Sofosbuvir is metabolised by human cathepsin A (CatA), carboxylesterase 1 (CES1) and histidine triad nucleotide-binding protein 1 (Hint1). The active triphosphate is formed with stepwise phosphorylation by UMP-CMP kinase and NDP kinase.[2]
Inducer of	Sofosbuvir and GS-331007 are not inducers of CYP450, UGT1A1 or drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT1, and BSEP).[2]
Inhibitor of	Sofosbuvir and GS-331007 are not inhibitors of CYP450, UGT1A1 or drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT1, and BSEP).[2] GS-331007 showed no inhibition of the renal transporters OAT1, OAT3, OCT2, andMATE1. [2]
Transported by	Sofosbuvir, but not GS-331007, is a substrate of P-gp and BCRP.

References

Unless otherwise stated (see below), information is from:
Sovaldi® Summary of Product Characteristics, Gilead Sciences Ltd.
Sovaldi® US Prescribing Information, Gilead Sciences.

1. Lawitz E, *et al*. 2012, *J Hepatol*, 56(S2): S445-S446 (Abstract 1130).
2. Mathias A. 14th International Workshop on Clinical Pharmacology of HIV Therapy, Session 5