Details

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Sofosbuvir (SOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name</td>
<td>Sovaldi®</td>
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<tr>
<td>Class</td>
<td>NS5B nucleotide polymerase inhibitor</td>
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<tr>
<td>Molecular Weight</td>
<td>529.45</td>
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<tr>
<td>Structure</td>
<td><img src="image" alt="Sofosbuvir Structure" /></td>
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</table>

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 200-400 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**
85% (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. Safety data are limited in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²] or end stage renal disease (ESRD) requiring haemodialysis. Sofosbuvir can be used in these patients with no dosage adjustment when no other treatment options are available.
**Hepatic Impairment**

No dose adjustment of sofosbuvir is warranted in mild, moderate or severe hepatic impairment. Population pharmacokinetics analysis in adult HCV-infected patients indicated that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and GS-331007.

**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, and MATE1.\(^2\)

*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.


2. Mathias A. 14\(^{th}\) International Workshop on Clinical Pharmacology of HIV Therapy, Session 5