Daclatasvir PK Fact Sheet

Details

**Generic Name**  
Daclatasvir

**Trade Name**  
Daklinza®

**Class**  
NS5A replication complex inhibitor

**Molecular Weight**  
739 (812 as dihydrochloride)

**Structure**

![Chemical Structure of Daclatasvir](image)

Summary of Key Pharmacokinetic Parameters

**Linearity/non-linearity**  
Pharmacokinetics increased in a largely dose-proportional manner from 1 to 100 mg, though exposures overlapped between 60 and 100 mg. 

**Steady State**  
Steady state was achieved after 4 days of once daily administration.

**Plasma Half life**  
12-15 h

**Cmax**  
1534 ng/ml (60 mg once daily)

**Cmin**  
232 ng/ml (60 mg once daily)

**AUC**  
14122 ng.h/ml (60 mg once daily)

**Interindividual Variation**  
~20-40% (60 mg once daily, 14 days, n=4)

**Bioavailability**  
67%

**Absorption**  
In healthy subjects, administration of daclatasvir 60 mg tablet after a high-fat meal decreased daclatasvir Cmax and AUC by 28% and 23%, respectively, compared with fasting conditions. Administration after a light meal resulted in no reduction in daclatasvir exposure.

**Protein Binding**  
>99%

**Volume of Distribution**  
47 L

**CSF:Plasma ratio**  
Not studied

**Semen:Plasma ratio**  
Not studied

**Renal Clearance**  
Minimal (6.6% of total daily dose)

**Renal Impairment**  
The pharmacokinetics of daclatasvir (60 mg single oral dose) were studied in non-HCV infected subjects with renal impairment. Daclatasvir unbound AUC was estimated to be 18%, 39% and 51% higher for subjects with creatinine clearance (CLcr) values of 60, 30 and 15 ml/min, respectively, relative to subjects with normal renal function. Subjects with end-stage renal disease requiring hemodialysis had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to subjects with normal renal function.

**Hepatic Impairment**  
The pharmacokinetics of daclatasvir (30 mg single oral dose) were studied in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with unimpaired subjects. Cmax and AUC of total daclatasvir (free and protein-bound) were lower in subjects with hepatic impairment; however, hepatic impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir.
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Metabolism and Distribution

<table>
<thead>
<tr>
<th>Metabolised by</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducer of</td>
<td>Very weak inducer of CYP3A4</td>
</tr>
<tr>
<td></td>
<td>(no dose adjustment of coadministered CYP3A4 substrates necessary)</td>
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<tr>
<td>Inhibitor of</td>
<td>P-gp, OATP 1B1, BCRP.</td>
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<tr>
<td></td>
<td>In vitro inhibitor of OAT1, OAT3 and OCT2, (not expected to have a clinical effect on the pharmacokinetics of substrates of these transporters).</td>
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<td>Does not inhibit CYP3A4 (^2), or CYPs 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 in vitro.</td>
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<tr>
<td>Transported by</td>
<td>P-gp</td>
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</tbody>
</table>

References

Unless otherwise stated (see below), information is from:
Daklinza® Summary of Product Characteristics, Bristol-Myers Squibb.
Daklinza® US Prescribing Information, Bristol-Myers Squibb Co.