Daclatasvir PK Fact Sheet

Details

Generic Name          Daclatasvir
Trade Name            Daklinza®
Class                 NS5A replication complex inhibitor
Molecular Weight      739 (812 as dihydrochloride)
Structure

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 [1].

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) [1]

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 haemodialysis 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
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impairment did not have a clinically significant effect on the free drug concentrations of daclatasvir.

### Metabolism and Distribution

<table>
<thead>
<tr>
<th>Metabolised by</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inducer of</strong></td>
<td>Very weak inducer of CYP3A4 (no dose adjustment of coadministered CYP3A4 substrates necessary)</td>
</tr>
<tr>
<td><strong>Inhibitor of</strong></td>
<td>P-gp, OATP1B1/B3, BCRP. Does not inhibit CYP3A4 (^2), or CYPs 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 in vitro.</td>
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<tr>
<td><strong>Transported by</strong></td>
<td>P-gp</td>
</tr>
</tbody>
</table>

### References

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