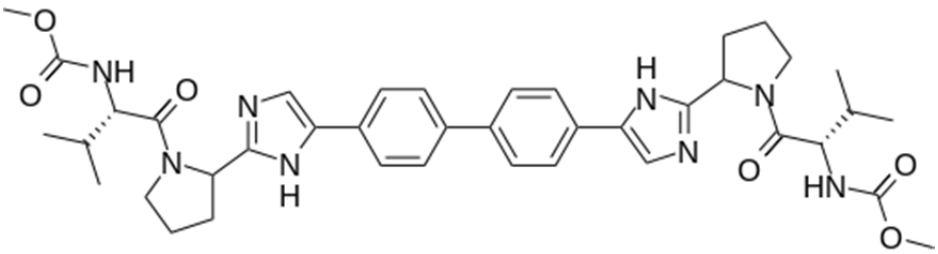
Daclatasvir PK Fact Sheet

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 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.

Metabolism and Distribution

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

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.

1. Nettles RE, *et al*. 2011, *Hepatology*, 54(6):1956-1965.
2. Amblard F, *et al*. 2013, *Bioorg Med Chem Lett*, 23: 2031-2034.