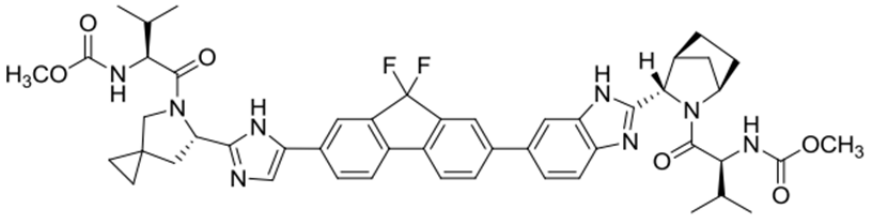
Ledipasvir PK Fact Sheet

Details

Generic Name	Ledipasvir
Trade Name	Harvoni® (coformulated with sofosbuvir)
Class	HCV NS5A inhibitor
Molecular Weight	889.0
Structure	

Summary of Key Pharmacokinetic Parameters

Ledipasvir is available in a fixed-dosed combination product with sofosbuvir.

Linearity/non-linearity	Ledipasvir AUC is dose proportional over the dose range of 3-100 mg.
Steady state	Not stated
Plasma half life	47 h
Cmax	323 ng /ml (mean, based on population PK analysis)
Cmin	Not stated
AUC	7290 ng.h/ml (mean, based on population PK analysis)
Bioavailability	Not determined
Absorption	Relative to fasting conditions, the administration of a single dose of ledipasvir/sofosbuvir with a moderate fat or high fat meal had no effect on exposure of ledipasvir.
Protein Binding	>99.8%
Volume of Distribution	Not determined
CSF:Plasma ratio	Not determined
Semen:Plasma ratio	Not determined
Renal Clearance	~1%
Renal Impairment	No dose adjustment of ledipasvir/sofosbuvir is required for patients with mild or moderate renal impairment. The pharmacokinetics of ledipasvir were studied with a single dose of 90 mg ledipasvir in HCV negative patients with severe renal impairment (eGFR <30 mL/min by Cockcroft-Gault, median [range] CrCl 22 [17-29] mL/min). No clinically relevant differences in ledipasvir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment. The safety of ledipasvir/sofosbuvir has not been assessed in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis. No dosage recommendation can be given for ledipasvir/sofosbuvir for patients with severe renal impairment or with ESRD due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.
Hepatic Impairment	No dose adjustment of ledipasvir/sofosbuvir is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C). Ledipasvir plasma exposure was similar in patients with severe hepatic impairment and control patients with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis had no clinically relevant effect on the exposure to ledipasvir.

Metabolism and Distribution

Metabolised by	In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Biliary excretion of unchanged ledipasvir is a major route of elimination.
Inducer of	Weak inducer of CYP3A4, CYP2C and UGT1A1 in vitro.
Inhibitor of	Intestinal CYP3A4 and UGT; P-gp, BCRP. Does not inhibit OATP1B1, OATP1B3, BSEP, OCT1, OCT2, OAT1, OAT3, MATE1, MRP2 or MRP4.
Transported by	P-gp, BCRP. Ledipasvir is not a substrate for OCT1, OATP1B1 or OATP1B3.

References

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