Supplemental Digital Content

Physiologically-Based Pharmacokinetic Modeling for Predicting the Effect of Intrinsic and Extrinsic Factors on Darunavir or Lopinavir Exposure Co-administered with Ritonavir

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Supplemental Table 1 (S1). PBPK model input parameters for LPV, DRV, and RTV.

Parameter	LPV	DRV	RTV[10]
MW	628.8[1]	547.7[2]	721.0
Log P	4.2 (pred[A])	2.5[3]	3.9
pKa	Neutral[1]	Neutral[B,4]	1.8 (b); 2.8 (b)
fu	0.01[1]	0.05[2]	0.02
B/P	0.75 (pred[C])	0.65 [D,5]	0.58
Absorption			
fa	1[E,6]	1[E,2]	1
[1/h]	0.57[7]	1.04[8]	0.22
Distribution			
PBPK model	minimal	minimal	minimal
Vss [L/kg]	0.82 (pred[C])	1.7 [F,9]	0.40 (pred)
Kp scalar	0.098[G]	1 (default)	0.048
Elimination			
CYP2D6			Vmax: 0.7; Km: 1
CYP3A4	CLint: 93.4[H]	CLint: 182[I]	Vmax: 1.37; Km: 0.07

CYP3A5			Vmax: 1; Km: 0.05
CLr	0.15[6]	0.30[I]	0.27
Additional CL		Systemic: 6.5 L/h[I]	HLM: 50
Interaction - Inhibition			
CYP2B6		Ki: 500[2]	Ki: 1.3
CYP2C9		Ki: 52[2]	Ki: 1.22
CYP2C19		Ki: 25[2]	
CYP2D6		Ki: 41[2]	Ki: 0.06
CYP3A4	Kapp: 0.41; Kinact: 1[J]	Ki: 0.4[2]	Kapp: 0.25; Kinact: 19.8
CYP3A5	Kapp: 1; Kinact: 1[J]	Ki: 0.4[2]	Kapp: 0.25; Kinact: 19.8
Interaction - Induction			
CYP3A4			Indmax: 68.5; IndC50: 1
CYP3A5			Indmax: 68.5; IndC50: 1

B base/basic, *B/P* blood:plasma partition ratio, *CL* clearance, *CLint* intrinsic clearance [µL/min/mg protein], *CLr* renal clearance [L/h], *CYP* cytochrome P450, *DRV* darunavir, *fa* fraction absorbed, *fu* fraction of unbound drug in plasma, *HLM* human liver microsomes, *IndC50* inducer concentration that yields half-maximal induction [µmol/L], *Indmax* maximum fold induction, *ka* absorption rate constant [h^{-1}], *Kapp* concentration of mechanism-based inhibitor associated with half-maximal inactivation rate [µmol/L], *Ki* inhibitor concentration that yields half-maximal inhibition [µmol/L], *Kinact* inactivation rate of given enzyme [h^{-1}], *Km* Michaelis-Menten constant [µmol/L], *Kp* partition coefficient, *log P* logarithm of octanol-water partition coefficient, *LPV* lopinavir, *MW* molecular weight [g/mol], *PBPK* physiologically-based pharmacokinetic, *pKa* negative decadal logarithm of acid dissociation constant, *pred* predicted, *RTV* ritonavir, *Vmax* maximum rate of metabolite formation [pmol/min/mg microsomal protein], *Vss* volume of distribution at steady state [L/kg]

A GastroPlus™ (v.8) prediction, based on the molecular structure of lopinavir.

B pKa of 2.4 (basic) and 13.6 (acidic) indicates the molecule is not ionized at the physiologically relevant pH range

C Simcyp® prediction, based on the physicochemical properties of the drug.

D Based on range of mean blood to plasma concentration ratio of total radioactivity ranging from 0.59 to 0.70 with darunavir/ritonavir

E Based on absolute darunavir/ritonavir bioavailability of 82% and 20% of oral lopinavir recovered unchanged in the feces.

F The Vss predicted from the physicochemical properties of DRV (0.7 L/kg) over-predicted boosted DRV C_{max}, and underpredicted C_{min}. Therefore, a Vss of 1.7 L/kg, which derives from intravenous administration of boosted DRV[9], was applied to the model.

G The Parameter Estimation Tool provided within the software was used to fit the Kp scalar to observed data following oral administration of 400 mg of unboosted LPV[1].

H Calculated from the observed apparent clearance following oral administration of single doses of 400 mg and 800 mg of unboosted LPV[1]. The intrinsic clearance LPV was calculated using Simcyp®'s retrograde model.

I Clearance of unboosted DRV was described using data based on intravenous infusion of 150 mg unboosted DRV[2]. From a variety of CYP enzymes, only CYP3A4 shows activity towards DRV[2]. Therefore, initially, based on minimal real clearance[2], we assigned 98.8% of total drug elimination to CYP3A4, and 1.2% to renal elimination.

Preliminary simulations using this model showed an approximately 10-fold over-prediction of the effect of RTV on the exposure of DRV (data not shown). Subsequent refinement of the DRV

PBPK model, compared with the multiple dose pharmacokinetics of boosted DRV and DRV-ketoconazole interaction data[11], included a stepwise reduction of the fm (CYP3A4) from 98.8% (initial PBPK model) to 85%, 80%, 75%, 70%, and 60%, with additional non-CYP clearances of 0%, 13.8%, 18.8%, 23.8%, 28.8%, and 38.8%. For all these DRV PBPK models, renal elimination accounted for 1.2% of total elimination (see note 5).

The DRV PBPK model constituting of a fm (CYP3A4) of 75% (182 µL/min/mg protein), an additional non-CYP clearance of 23.8% (6.5 L/h), and a renal clearance of 1.2% (0.3 L/h), yielded best simulation results, and was subsequently used for all further simulations.

J Considering mechanism-based inhibition of CYP3A4 (Kapp = 0.41 µmol/L; kinact = 6 h^{-1}) and CYP3A5 (Kapp = 1 µmol/L; Kinact = 3 h^{-1}) by unboosted LPV[12] yielded predicted LPV steady-state plasma concentrations exceeding those of boosted LPV (data not shown). To account for the obvious over-prediction of mechanism-based inhibition by recombinant CYP3A4 and CYP3A5, and since no other data are available, the inhibition potency of unboosted LPV was "arbitrarily" decreased in a stepwise manner, with kinact values of 6 h^{-1} (initial value)[12], 4 h^{-1}, 2 h^{-1}, 1 h^{-1}, and 0.5 h^{-1} for both CYP3A4 and CYP3A5. Between Kinact values of 4 h^{-1} and 2 h^{-1}, the model was very sensitive, and the predicted oral clearance of LPV under steady state conditions was increased markedly. However, at Kinact values of ≤ 1 h^{-1}, sensitivity of the model towards Kinact was decreased, and a further reduction of Kinact had no substantial impact on the predicted exposure of unboosted LPV under steady state conditions. Therefore, we used a Kinact value of 1 h^{-1} for all further simulations. Since LPV is always administered with RTV, and RTV is a much stronger mechanism-based inhibitor compared to LPV ($Kinact_{RTV}$ = 19.8 h^{-1}, $Kinact_{LPV}$ = 6 h^{-1} [12]), it is highly likely that the DDI potential of the LPV/RTV combination is attributed to the characteristics of RTV rather than LPV.

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