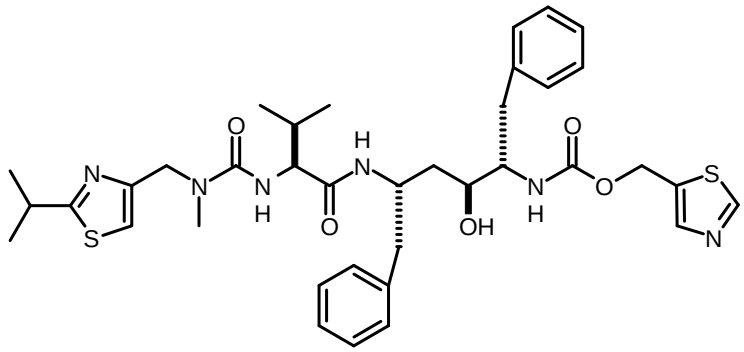
Ritonavir PK Fact Sheet

Details

Generic Name	Ritonavir
Trade Name	Norvir®
Class	Protease Inhibitor
Molecular Weight	720.95
Structure	

Summary of Key Pharmacokinetic Parameters

Steady state	Upon multiple dosing, ritonavir accumulation is slightly less than predicted from a single dose due to a time and dose-related increase in apparent clearance (Cl/F). Trough concentrations of ritonavir decrease over time, possibly due to enzyme induction, but appeared to stabilise by the end of 2 weeks.
Plasma half life	3-5 h (600 mg twice daily) ~5 h (100 mg twice daily or once daily)
Cmax	11.2 ± 3.6 µg/ml (600 mg twice daily) 0.84 ± 0.39 µg/ml (100 mg once daily) 0.89 µg/ml (100 mg twice daily)
Cmin	3.7 ± 2.6µg/ml (600 mg twice daily) 0.08 ± 0.04 µg/ml (100 mg once daily) 0.22 µg/ml (100 mg twice daily)
AUC	77.5 ± 31.5 µg/ml.hr (600 mg twice daily) 6.6 ± 2.4 µg/ml.hr (100 mg once daily) 6.2 µg/ml.hr (100 mg twice daily)
Bioavailability	Not determined
Absorption	Food slightly decreases the bioavailability of the ritonavir tablet. Administration of ritonavir (100 mg single dose) with a moderate fat meal (857 kcal, 31% calories from fat) or a high fat meal (907 kcal, 52% calories from fat) was associated with a mean decrease of 20-23% in ritonavir AUC and Cmax.
Protein Binding	98-99%
Volume of Distribution	20-40 L (600 mg single dose)
CSF:Plasma ratio	0.0-0.52 [1]
Semen:Plasma ratio	<0.04 [2]
Renal Clearance	3.5% as unchanged drug

Renal Impairment	Renal clearance of ritonavir is negligible; a decrease in total body clearance is not expected in renal impairment. There are currently no data specific to this patient population
Hepatic Impairment	Pharmacokinetic data indicate that no dose adjustment is necessary in mild to moderate hepatic impairment. Ritonavir should not be given to patients with severe hepatic impairment. Ritonavir should not be given as a pharmacokinetic enhancer to patients with decompensated liver disease. In the absence of pharmacokinetic studies in patients with stable severe hepatic impairment (Child Pugh Grade C) without decompensation, caution should be exercised as increased levels of the co-administered PI may occur

Metabolism and Distribution

Metabolised by	CYP3A, CYP2D6
Inducer of	CYP1A2, CYP2C8, CYP2C9 and CYP2C19, MRP1 expression [3]
Inhibitor of	CYP3A, CYP2D6, P-glycoprotein [4], MRP1 [5], OATP-C [6], BCRP [7]
Transported by	P-glycoprotein [4] , MRP1 [5]

References

Unless otherwise stated (see below), information is from:
Norvir® Tablets Summary of Product Characteristics, AbbVie Ltd.
Norvir® Tablets US Prescribing Information, AbbVie Inc.

1. Antinori A *et al*. Antiretroviral distribution in cerebrospinal fluid and viral resistance in HIV-infected patients. 9th Conference on Retroviruses and Opportunistic Infections, Seattle, February 2002. Abst 438W.
2. Taylor S, Back DJ, Drake SM, *et al*. Antiretroviral drug concentrations in semen of HIV-infected men: differential penetration of indinavir, ritonavir and saquinavir. *J Antimicrob Chemother.* 2001; 48(3): 351-354.
3. Thomas S. Drug Transporters relevant to HIV therapy, *J HIV Ther.* 2004; 9(4): 92-96.
4. Lee C, Gottesman M, Cardarelli CO, *et al*. HIV-1 protease inhibitors are substrates for the MDR1 multidrug transporter. *Biochemistry.* 1998; 37(11): 3594-3601.
5. Srinivas R, Middlemas D, Flynn P, Fridland A. Human immunodeficiency virus protease inhibitors serve as substrates for multidrug transporter proteins MDR1 and MRP1 but retain antiviral efficacy in cell lines expressing these transporters. *Antimicrob Agents Chemother.* 1998; 42(12): 3157-3162.
6. Tirona R, Leake B, Wolkoff AW, Kim RB. Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampicin mediated pregnane X receptor activation. *J Pharmacol Exp Ther.* 2003; 304(1): 223-228.
7. Gupta A, Zhang Y, Unadkat JD, Mao Q. HIV protease inhibitors are inhibitors but not substrates of the human breast cancer resistance protein (BCRP/ABCG2). *J Pharmacol Exp Ther.* 2004; 310(1): 334-341.