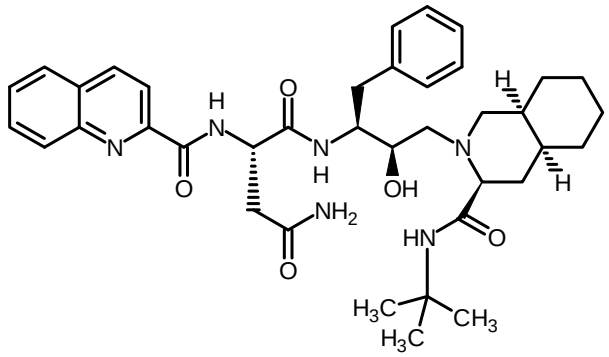
Saquinavir PK Fact Sheet

Details

Generic Name	Saquinavir
Trade Name	Invirase®
Class	Protease Inhibitor
Molecular Weight	670.86 (as free base)
Structure	

Summary of Key Pharmacokinetic Parameters

Plasma half life	7-12 h [1]
Cmax	5208 (1536-14369) ng/ml (1000/100mg saquinavir/ritonavir twice daily; tablet, with food)
Cmin	1179 (334-5176) ng/ml (1000/100mg saquinavir/ritonavir twice daily; tablet, with food)
AUC	69852 ng/ml.hr (24h) (1000/100mg saquinavir/ritonavir twice daily; tablet, with food)
Bioavailability	4% (600 mg single dose alone, hard capsules)
Absorption	Saquinavir/ritonavir should be administered with or after food. In a cross-over study in 22 HIV-infected patients treated with saquinavir/ritonavir (1000/100 mg twice daily) and receiving three consecutive doses under fasting conditions or after a high-fat, high-calorie meal (46 g fat, 1,091 Kcal), the AUC, Cmax and Ctrough values of saquinavir under fasting conditions were about 70% lower than with a high-fat meal. All but one of the patients achieved Ctrough values of saquinavir above the therapeutic threshold (100 ng/ml) in the fasted state. There were no clinically significant differences in the pharmacokinetic profile of ritonavir in fasting and fed conditions but the ritonavir Ctrough (geometric mean 245 vs 348 ng/ml) was lower in the fasting state compared to the administration with a meal.
Protein Binding	~97%
Volume of Distribution	700 L (12 mg IV dose)
CSF:Plasma ratio	Negligible
Semen:Plasma ratio	0.04 [1]
Renal Clearance	1-3%
Renal Impairment	Renal clearance is a minor elimination pathway. No dosage adjustment required in mild/moderate renal impairment; caution should be exercised in severe renal impairment
Hepatic Impairment	No dosage adjustment necessary in mild hepatic impairment; Caution should be exercised in patients with moderate hepatic impairment. The use of saquinavir in decompensated hepatic impairment is contraindicated

Metabolism and Distribution

Metabolised by	CYP3A4
Inducer of	N/A
Inhibitor of	P-glycoprotein [2], MRP1 [3] , BCRP (*in vitro*)[4], OATP-C [5]
Transported by	P-glycoprotein [2], MRP1 [3], MRP2 [6], hOATPs [7]

References

Unless otherwise stated (see below), information is from:
Invirase® Summary of Product Characteristics, Roche Products Ltd.
Invirase® Prescribing Information, Genentech Inc.

1. 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.
2. 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.
3. 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.
4. Weiss J, Rose J, Storch CH, *et al.* Modulation of human BCRP (ABCG2) activity by anti-HIV drugs. *J Antimicrob Chemother.* 2007; 59(2): 238-245.
5. Tirona R, Leake B *et al* Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampicin mediated pregnane X receptor activation. *J Pharmacol Exp Ther* 304: 223-228.
6. Huisman M, Smit J, Crommentuyn KM, *et al*. Multidrug resistance protein 2 (MRP2) transports HIV protease inhibitors, and transport can be enhanced by other drugs. *AIDS.* 2002; 16: 2295-2301.
7. Janneh O, Hartkoorn RC, Jones E, *et al*. Cultured CD4T cells and primary human lymphocytes express hOATPs: intracellular accumulation of saquinavir and lopinavir. *Br J Pharmacol.* 2008; 155(6): 875-883.