

### Selected Properties of Saquinavir

<b>Other names</b>	Invirase®, Ro 31-8959  Fortovase® soft gel capsule – <b>sale and distribution discontinued in 2006</b>
<b>Manufacturer</b>	Hoffmann-La Roche
<b>Pharmacology/Mechanism of Action</b>	HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.
<b>Activity</b>	In vitro IC50 1-30 nM, IC90 5-80 nM; additive to synergistic effect with AZT, ddI, ddC, 3TC, d4T, nevirapine WT IC50: 0.001-0.0063 uM (Phenosense)
<b>Resistance - genotypic</b>	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: G48V, L90M Minor: L10I/R/V, I54V/L, A71V/T, G73S, V77I, V82A, I84V <i>*as major &amp; minor mutations accumulate, susceptibility to PIs decreases</i>
<b>Resistance - phenotypic</b>	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ ( <a href="http://hivdb.stanford.edu/">http://hivdb.stanford.edu/</a> ): 48V, 82A: 8.8-fold ↑ 48V, 90M: 19-fold ↑ 48V, 54V, 82A: 147-fold ↑ 48V, 54V, 82A, 90M: 322-fold ↑ 48V, 54V, 82A, 84V: 583-fold ↑
<b>Cross-Resistance</b>	Varying degrees of cross-resistance with other PI's
<b>Oral Bioavailability</b>	a) hard-gel capsule (Invirase): F= 4% with <b>food</b> - best with <b>fatty</b> foods -F=↓ 18x if taken when fasting -low F due to-limited absorption and extensive first-pass metabolism b) film-coated tablet (Invirase): Similar bioavailability was demonstrated when Invirase 500 mg film coated tablets (2 x 500 mg) and Invirase 200 mg capsule (5 x 200 mg) were administered with low dose ritonavir (100 mg) under fed conditions. c) soft-gel capsule (Fortovase): F= 12%
<b>Effect of Food</b>	Invirase® (hard-gel capsule): Heavy breakfast (48g protein, 60g carbohydrate, 57g fat; 1006 kcal): <ul style="list-style-type: none"> <li>• AUC substantially ↑ (from 24 ng·h/mL to 161 ngAh/mL)</li> <li>• ↑ Tmax from 2.4 hours to 3.8 hours</li> <li>• ↑ Cmax from 3.0 ng/mL to 35.5 ng/mL.</li> <li>• The effect of food has been shown to be present for up to 2 hours after food intake.</li> </ul> Invirase® (500 mg tablet):

	<p>21 HIV patients on SQV/r 1000/100mg BID given within 15min of a meal underwent a kinetic study to compare the effect of a high fat meal (55g of fat/1291 kcal) VS a standard meal (15g of fat/651 kcal) on SQV plasma levels:</p> <ul style="list-style-type: none"> <li>• High Fat Meal: AUC 29,365ng.h/ml; Cmax: 4360ng/ml; Ctrough: 994ng/ml</li> <li>• Standard Meal: AUC 20,332ng.h/ml; Cmax: 3240ng/ml; Ctrough: 800ng/ml</li> <li>• SQV levels were mildly decreased with a standard meal VS high fat meal. All patients had Ctrough &gt; cut off of 100ng/ml</li> </ul> <p>The authors conclude that SQV should be given with food, but the fat content of the meal is not critical [Boffito et al. ICAAC 2007].</p> <p>Grapefruit juice:</p> <ul style="list-style-type: none"> <li>• AUC doubled when Invirase taken with double-strength grapefruit juice</li> <li>• AUC ↑ 30% when take with regular grapefruit juice</li> </ul>
<b>Protein Binding</b>	>98%
<b>Vd</b>	- 700 L - considerable tissue binding
<b>Tmax</b>	2-4 hours
<b>serum T ½</b>	13.2 hours
<b>Drug Concentrations</b>	<p>a) hard-gel capsules (Invirase)</p> <ul style="list-style-type: none"> <li>• 600 mg q8h: Cmax: 253 ng/mL; AUC 757.2 ng.h/mL</li> <li>• 1000 mg/100 mg ritonavir BID: Cmin 371 ng/mL, AUC 14607 ng.h/mL</li> <li>• 400 mg/400 mg ritonavir BID: Cmin 480 ng/mL, AUC 16000 ng.h/mL</li> </ul> <p>b) film-coated tablets (Invirase):</p> <ul style="list-style-type: none"> <li>• A gender difference was observed, with females showing higher saquinavir exposure than males (mean AUC increase of 56%, mean Cmax increase of 26%), in the relative bioavailability study comparing saquinavir 500 mg film coated tablets to the saquinavir 200 mg capsules in combination with ritonavir. There was no evidence that age and body weight explained the observed gender difference in concentrations.</li> </ul> <p>b) soft-gel capsules (Fortovase):</p> <ul style="list-style-type: none"> <li>• 1200 mg q8h: Cmin 216 ng/mL, AUC 21747 ng.h/mL</li> <li>• 1000 mg/100 mg ritonavir BID: Cmin 433 ng/mL, AUC 19085 ng.h/mL</li> </ul> <p>In vivo intracellular accumulation: cell/plasma ratio 4.94-9.45 (saquinavir alone), 2.74-4.01 when dosed with ritonavir.</p>

<b>Minimum target trough concentrations (for wildtype virus)</b>	0.1 mg/mL
<b>CSF (% of serum)</b>	-negligible (n=2)  2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
<b>Metabolism</b>	Extensive first-pass metabolism; metabolized to inactive mono- and dihydroxylated metabolites by cytochrome P450 (90% by CYP3A4 isoenzyme). Saquinavir is also a substrate of p-glycoprotein (Pgp). Saquinavir is a weak inhibitor of CYP3A4.
<b>Excretion</b>	-nonrenal -88% biliary/fecal - <4% excreted in urine
<b>Dosing – Adult</b>	<b>Note: Fortovase® and Invirase® are not bioequivalent and cannot be used interchangeably.</b>  <b>Boosted with ritonavir (recommended):</b> <b>Hard-gel capsules or tablets*:</b> SQV 1000 mg po BID + RTV 100 mg po BID SQV 400 mg po BID + RTV 400 mg po BID  Take within 2 hours of a <b>meal or substantial snack, even when boosted with ritonavir</b> . Take ritonavir at the same time as saquinavir.
<b>Dosing – Pediatric</b>	<b>Neonatal/Infant:</b> unknown  <b>Pediatric:</b> SQV-sgc 50 mg/kg/dose q 8h as a single PI therapy SQV-sgc 33 mg/kg/dose q 8h as usual therapy with nelfinavir
<b>Special instructions for pediatric patients</b>	<ul style="list-style-type: none"> <li>• wear sunscreen (photosensitivity &lt; 2% patients)</li> <li>• give within 2 hours of a full meal or large snack to increase absorption</li> <li>• give with grapefruit juice to increase absorption (if not on ritonavir)</li> <li>• unpalatable (very bitter)</li> <li>- <b>Invirase® HGC</b> contains powder in capsule that can be opened and sprinkled on food, water, simple syrup, baby formula or jelly jam, but has unpalatable taste.</li> <li>• In an open-label, randomized, 4 period study in adults, the bioavailability of 1000 mg opened saquinavir capsules suspended in simple syrup, baby formula and jelly jam (plus ritonavir 100 mg oral solution) was approximately 10%, 60% and 40% higher, respectively, than 1000 mg unopened saquinavir capsules plus ritonavir. In terms of palatability, saquinavir suspended in simple syrup or jelly jam ranked higher than saquinavir suspended in baby food.(McKay et al. 2007).</li> </ul> <p>- <b>Fortovase® SGC</b> contains liquid or gel in capsule - 6 x 200 mg Fortovase whole caps mixed with 50 mL of whole milk or Advera nutritional supplement took 5-15 minutes to dissolve when heated to 40, 60 or 80 degrees C. The mixture remained in solution for up to 1 hour at room temperature. If</p>

	refrigerated for 24 hours, it turned into a gel, but reliquified after reheating to 30 degrees C. The drug was still stable at 24 hours. (data on file, Hoffmann-La Roche)
<b>Adjust in Liver Dysfunction</b>	<p>No dosage recommendations available; use with caution in mild to moderate hepatic impairment. Contraindicated in severe hepatic impairment.</p> <p>The steady-state kinetics of saquinavir 1000/ritonavir 100 mg BID plus 2-3 NRTIs was investigated in treatment-experienced HIV patients with moderate hepatic impairment (n=7, all HCV coinfecting, Child-Pugh grade B) and matched controls with normal liver function. In patients with hepatic impairment, saquinavir and ritonavir AUC was ↓ 35% and 25%, respectively versus controls. Dose adjustments are not required in patients with moderate liver disease.[Chang et al. 2010]</p>
<b>Adjust in Renal Failure/Dialysis</b>	No dosage adjustment necessary. Administer regardless of dialysis schedule.
<b>Toxicity</b>	<p><b>GI:</b> diarrhea, abdominal pain, nausea  <b>CNS:</b> headache, paresthesias</p> <p>Derm: photosensitivity reactions (use sunscreen)</p> <p><b>HEPATIC:</b> mild ↑ LFTs</p> <p><b>Other:</b> Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.</p> <p>Potential risk of QT prolongation; avoid use in patients already taking medications known to cause QT interval prolongation such as Class IA (such as quinidine,) or Class III (such as amiodarone) antiarrhythmic drugs, or in patients with a history of QT interval prolongation [FDA advisory update, Feb 23, 2010].</p>
<b>Pregnancy &amp; Lactation</b>	<p>Pregnancy risk category B. Inadequate drug levels when Fortovase® is used alone. Use Fortovase® (SQV-sgc) OR Invirase® (SQV-hgc) 1000 mg BID + ritonavir 100 mg BID. Considered a preferred PI combination in pregnancy.</p> <p>Saquinavir exposure is not reduced in 3<sup>rd</sup> trimester of pregnancy when administered as 1000 mg (2 x 500 mg tablets)/ritonavir 100 mg BID. No dose adjustment required (Van der Lugt et al. 2008)</p>
<b>Drug Interactions</b>	<p>Saquinavir is a substrate and weak inhibitor of CYP3A4; saquinavir is also a substrate of P-glycoprotein. Therefore, drugs that affect CYP3A4 and/or Pgp, may modify the pharmacokinetics of saquinavir. Similarly, saquinavir might also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or Pgp. See Separate Drug Interaction Table</p>
<b>Baseline Assessment</b>	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia),

	and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile.
<b>Routine Labs</b>	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months.
<b>Dosage Forms</b>	200mg (yellow & green) hard-gel capsule (Invirase®); DIN 02216965  500 mg (greyish-orange) film-coated tablets (Invirase®); DIN 02279320, bottles of 120.  200mg (beige) soft-gel capsule (Fortovase®); DIN 02239083 ** <i>discontinued in 2006</i>
<b>Storage</b>	Invirase®(hard-gel capsules and tablets): store at room temperature. Fortovase® (soft-gel caps): store in refrigerator until dispensed; once brought to room temperature, stable for 3 months. ** <i>discontinuation in 2006</i>

#### References:

Boffito M, Singh K, Higgs C, Chaikan A, Back D, Nelson M, et al. Effect of different meals on the pharmacokinetic profile of saquinavir 500 mg tablet/ritonavir 1000 mg/100 mg BID in HIV-infected individuals [abstract A-1423]. 47<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, September 17-20, 2007.

Chang L, Kreuzer C, Farha R, Abt M, Baher L, Tebas P et al. Effect of moderate liver impairment on the multiple-dose pharmacokinetics of ritonavir-boosted saquinavir in HIV patients [abstract WEPE0093]. XVIII International AIDS Conference, Vienna, Austria, July 18-23, 2010.

Ford J, Khoo SH, Back DJ. The intracellular pharmacology of antiretroviral protease inhibitors. JAC 2004 (advance on-line publication).

Hoffmann-La Roche Limited. Invirase® Product monograph. Mississauga, Ont. July 22, 2008.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

McKay D, Holmes B, Zandt H, Choudhury S. Relative bioavailability and palatability of ritonavir-boosted opened Invirase capsules suspended in three food vehicles compared to ritonavir-boosted unopened Invirase capsules [abstract 6]. 8<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy. Budapest, Hungary, April 16-18, 2007.

Van der Lugt J, Molto J, Hawkins D, Van de Ende I, Vogel M, Wyen C, et al. The influence of pregnancy on the pharmacokinetics of saquinavir boosted by low-dose ritonavir (1000/100 mg BID) [abstract O9]. 9<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy. New Orleans, USA, April 7-9, 2008.