

Selected Properties of Saquinavir

Other names	Invirase®, Ro 31-8959 Fortovase® soft gel capsule – sale and distribution discontinued in 2006
Manufacturer	Hoffmann-La Roche
Pharmacology/Mechanism of Action	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.
Activity	In vitro IC ₅₀ 1-30 nM, IC ₉₀ 5-80 nM; additive to synergistic effect with AZT, ddI, ddC, 3TC, d4T, nevirapine WT IC ₅₀ : 0.001-0.0063 uM (Phenosense)
Resistance - genotypic	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 & minor mutations accumulate, susceptibility to PIs decreases</i>
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): 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 ↑
Cross-Resistance	Varying degrees of cross-resistance with other PI's

<p>Oral Bioavailability</p>	<p>a) hard-gel capsule (Invirase): F= 4% with food - best with fatty foods -F=↓ 18x if taken when fasting -low F due to-limited absorption and extensive first-pass metabolism</p> <p>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%</p>
<p>Effect of Food</p>	<p>Invirase® (hard-gel capsule): Heavy breakfast (48g protein, 60g carbohydrate, 57g fat; 1006 kcal):</p> <ul style="list-style-type: none"> • AUC substantially ↑ (from 24 ng·h/mL to 161 ngAh/mL) • ↑ Tmax from 2.4 hours to 3.8 hours • ↑ Cmax from 3.0 ng/mL to 35.5 ng/mL. • The effect of food has been shown to be present for up to 2 hours after food intake. <p>Invirase® (500 mg tablet): 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"> • High Fat Meal: AUC 29,365ng.h/ml; Cmax: 4360ng/ml; Ctrough: 994ng/ml • Standard Meal: AUC 20,332ng.h/ml; Cmax: 3240ng/ml; Ctrough: 800ng/ml • SQV levels were mildly decreased with a standard meal VS high fat meal. All patients had Ctrough > cut off of 100ng/ml <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"> • AUC doubled when Invirase taken with double-strength grapefruit juice • AUC ↑ 30% when take with regular grapefruit juice
<p>Protein Binding</p>	<p>>98%</p>

Vd	- 700 L - considerable tissue binding
Tmax	2-4 hours
serum T_{1/2}	13.2 hours
Drug Concentrations	<p>a) hard-gel capsules (Invirase)</p> <ul style="list-style-type: none"> • 600 mg q8h: C_{max}: 253 ng/mL; AUC 757.2 ng.h/mL • 1000 mg/100 mg ritonavir BID: C_{min} 371 ng/mL, AUC 14607 ng.h/mL • 400 mg/400 mg ritonavir BID: C_{min} 480 ng/mL, AUC 16000 ng.h/mL <p>b) film-coated tablets (Invirase):</p> <ul style="list-style-type: none"> • A gender difference was observed, with females showing higher saquinavir exposure than males (mean AUC increase of 56%, mean C_{max} 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. <p>b) soft-gel capsules (Fortovase):</p> <ul style="list-style-type: none"> • 1200 mg q8h: C_{min} 216 ng/mL, AUC 21747 ng.h/mL • 1000 mg/100 mg ritonavir BID: C_{min} 433 ng/mL, AUC 19085 ng.h/mL <p>In vivo intracellular accumulation: cell/plasma ratio 4.94-9.45 (saquinavir alone), 2.74-4.01 when dosed with ritonavir.</p>
Minimum target trough concentrations (for wildtype virus)	0.1 mg/mL
CSF (% of serum)	-negligible (n=2)
Metabolism	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.

Excretion	-nonrenal -88% biliary/fecal - <4% excreted in urine
Dosing – Adult	<p>Note: Fortovase® and Invirase® are not bioequivalent and cannot be used interchangeably.</p> <p>Boosted with ritonavir (recommended): Hard-gel capsules or tablets*: SQV 1000 mg po BID + RTV 100 mg po BID SQV 400 mg po BID + RTV 400 mg po BID</p> <p>Take within 2 hours of a meal or substantial snack, even when boosted with ritonavir . Take ritonavir at the same time as saquinavir.</p>
Dosing – Pediatric	<p>Neonatal/Infant: unknown</p> <p>Pediatric: 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</p>

<p>Special instructions for pediatric patients</p>	<ul style="list-style-type: none"> • wear sunscreen (photosensitivity < 2% patients) • give within 2 hours of a full meal or large snack to increase absorption • give with grapefruit juice to increase absorption (if not on ritonavir) • unpalatable (very bitter) - Invirase® HGC contains powder in capsule that can be opened and sprinkled on food, water, simple syrup, baby formula or jelly jam, but has unpalatable taste. • 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). - Fortovase® SGC 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 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)
<p>Adjust in Liver Dysfunction</p>	<p>No dosage recommendations available; use with caution.</p>
<p>Adjust in Renal Failure/Dialysis</p>	<p>No dosage adjustment necessary. Administer regardless of dialysis schedule.</p>
<p>Toxicity</p>	<p>GI: diarrhea, abdominal pain, nausea CNS: headache, paresthesias</p> <p>Derm: photosensitivity reactions (use sunscreen)</p> <p>HEPATIC: mild ↑ LFTs</p> <p>Other: Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.</p>

Pregnancy & Lactation	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.
Drug Interactions	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
Baseline Assessment	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.
Routine Labs	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.
Dosage Forms	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 ** discontinued in 2006
Storage	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. ** discontinuation in 2006

References:

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Academic Copyright. M. Foisy, Pharm.D., Edmonton, AB, A. Tseng, Pharm.D. and Trish Marr, Pharm.D., Toronto, Ontario. Supplementary pediatric dosing & administration information prepared by Natalie Dayneka, Pharm.D., Children's Hospital of Eastern Ontario, Ottawa. Please note: This chart summarizes selected properties based on current available data. Please consult a health professional whenever beginning, stopping or modifying drug therapy. August 2007. Page 6 of 7

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