Saquinavir (Fortavase®, Invirase®)

Class:
Saquinavir is an HIV protease inhibitor.

Antiviral Activity:
Saquinavir has activity against HIV-1 and HIV-2.

Mechanism of Action:
Cleavage of polyproteins by the protease enzyme is an essential step in the HIV life cycle. After cleavage the immature virus proteins are assembled into particles which bud from the cell as mature, infectious virions. Protease inhibitors compete for the active cleavage site on the protease enzyme, blocking the cleavage of the polyproteins and thus the maturation of new viral particles.

Mechanism of Resistance:
Higher levels of protease inhibitor resistance result from the accumulation of multiple protease inhibitor-resistance mutations. There are many mechanisms of resistance. These include reduced binding affinity between the inhibitor and the protease enzyme, alterations in enzyme catalysis, effects on dimer stability, alterations in inhibitor binding kinetics and re-shaping of the active site.

Pharmacodynamics:
The fold change for IC$_{50}$ in the presence of 50% human serum for saquinavir was 14.7. The predicted fold change in 100% human serum is 28.

Pharmacokinetics:
Saquinavir hard gel capsules have a 4% bioavailability while the soft gel capsules have a 12% bioavailability. Saquinavir is approximately 97% bound to plasma proteins at concentrations up to 30 mcg/mL. The metabolism of saquinavir is mediated by the hepatic cytochrome P450 enzyme system, with the CYP3A4 isoenzyme accounting for more than 90%.

Adverse Effects:
The most common adverse effects associated with saquinavir are diarrhea, abdominal discomfort, and nausea.

Dosage:
Capsule 200mg
Tablet 500mg

Fortovase® and Invirase® are not bioequivalent and should not be used interchangeably. Only Fortovase® should be used to initiate therapy.

Adult:
Unboosted:
- Soft-gelatin capsule (Fortovase®) – 1200 mg three times daily with food
- Hard-gelatin capsule (Invirase®) – not recommended
Boosted:
Fortovase®: 1000 mg twice daily plus ritonavir 100 mg twice daily
Invirase®: 1000 mg twice daily plus ritonavir 100 mg twice daily (given together within 2 hours after a full meal)

Dose Adjustment of Fortovase® when in combination with other medications:
Delavirdine: Fortovase® 800 mg 3 times/day
Lopinavir and ritonavir (Kaletra™): Fortovase® or Invirase® 1000 mg twice daily
Nelfinavir: Fortovase®: 1200 mg twice daily
Pediatric: Currently being studied

Disease state based dosing:
Renal Impairment:
  no specified dose adjustment
Hepatic Impairment:
  no specified dose adjustment
  Use with caution in patients with moderate to severe hepatic insufficiency

Contraindications/Warnings/ Precautions:
Saquinavir is contraindicated with the following medications:
amiodarone, bepridil, flecainide, propafenone, quinidine, astemizole, terfenadine,
dihydroergotamine, ergonovine, ergotamine, methylergonovine, rifampin, cisapride,
pimozide, triazolam and midazolam.

Drug Interactions:
Saquinavir is metabolized by the cytochrome P450 enzyme system, predominately
CYP3A4 and is also a substrate of P-glycoprotein (Pgp). Therefore, medications that also
are substrates for CYP3A4 of Pgp may interact with saquinavir.

Pregnancy:
Category B: No evidence of risk in humans but studies inadequate.

Monitoring Requirements:
Blood glucose, LFTs, serum lipid profile

Brand names/Manufacturer:
Fortovase®/Hoffmann La Roche Inc
Invirase®/Hoffmann La Roche Inc