Indinavir (Crixivan®)

Class:
Indinavir is an HIV protease inhibitor.

Antiviral Activity:
Indinavir 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 virons. 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 multiple 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 indinavir is 2.1. The predicted fold change in 100% human serum is 3.5.

Pharmacokinetics:
Indinavir is rapidly absorbed in the fasted state. Meals high in fat, calories and protein decrease the area under the concentration-time curve (AUC) by 77 ± 8%. Indinavir is approximately 60% bound to human plasma proteins over the concentration range of 81 – 16,300 nM. Eighty-three (± 1) percent of indinavir is recovered in feces, 9.4% as unchanged drug. Cytochrome P450 3A4 is responsible for oxidative metabolism of indinavir.

Adverse Effects:
The most common adverse effects are nephrolithiasis, asymptomatic hyperbilirubinemia and hepatitis. Nephrolithiasis can be prevented with adequate hydration of at least 1.5 liters of liquids daily. Management of nephrolithiasis may require temporary discontinuation of indinavir for one to three days or permanent discontinuation.

Dosage:
Capsule 100mg, 200mg, 333mg, 400mg

Adults:
Unboosted: 800 mg every 8 hours on an empty stomach (one hour before or two hours after a meal)

Boosted: indinavir 800mg twice daily plus ritonavir 100-200mg twice daily OR
indinavir 400mg twice daily plus ritonavir 400mg twice daily

Dose adjustments with in combination with other medications:

Delavirdine, itraconazole, or ketoconazole: 600 mg every 8 hours
Efavirenz: 1000 mg every 8 hours
Lopinavir and ritonavir (Kaletra™): 600 mg twice daily
Nelfinavir: 1200 mg twice daily
Nevirapine: 1000 mg every 8 hours
Rifabutin: Reduce rifabutin to 1/2 the standard dose plus increase indinavir to 1000 mg every 8 hours

Pediatric: Currently being studied

Disease state based dosing:
Renal Impairment:
no specified dose adjustment
however, patients who experience nephrolithiasis/urolithiasis may need temporary interruption (1-3 days) or discontinuation of indinavir.
It is not known if indinavir is dialyzable by either peritoneal or hemodialysis
Mild to moderate hepatic insufficiency:
600 mg every 8 hours.

Contraindications/Warnings/ Precautions:
Indinavir is contraindicated with the following medications:
amiodarone, dihydroergotamine, ergonovine, ergotamine, methylergonovine, midazolam, triazolam, cisapride and pimozide

Drug Interactions:
Indinavir is primarily metabolized via CYP3A4. Therefore other medications that are primarily metabolized by CYP3A4 may interact with indinavir.

Pregnancy:
Category C: Risk unknown. Human studies inadequate.

Monitoring Requirements:
Blood glucose, serum lipid profile

Brand names/Manufacturer:
Crixivan®/Merck and Co Inc