**Selected Properties of Indinavir**

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| **Other names** | Crixivan® |
| **Manufacturer** | Merck Canada Inc. |
| **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** | IC95 in test systems: 25-100 nM<br>WT IC50: 0.0027-0.0171 uM (Phenosense) |
| **Resistance - genotypic** | Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations):<br>Major: M46I/L, V82A/F/T, I84V<br>Minor: L10I/R/V, K20M/R, L24I, V32I, M36I, I54V, A71V/T, G73S/A, V77I, L90M<br>**as major & minor mutations accumulate, susceptibility to PIs decreases* |
| **Resistance - phenotypic** | Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/):<br>M46I: 7.8-fold ↑ (intermediate resistance)<br>V82A/T/F/S with other mutations: 10- to 40-fold ↑ (high resistance)<br>I84V with other mutations: 10- to 100-fold ↑ (high resistance) |
| **Cross-Resistance** | Varying degrees of cross-resistance have been observed between indinavir sulfate and other HIV-protease inhibitors. |
| **Oral Bioavailability** | F= 30%<br>Best absorbed in acidic (normal) gastric pH. |
| **Effect of Food** | Food (784 kcal, 48.6 g fat, 31.3 g protein) ↓ AUC by 78%. Administration with lighter meals (e.g., dry toast with jelly, apple juice, and coffee with skim milk and sugar or a meal of corn flakes, skim milk and sugar) does not significantly affect indinavir AUC, Cmax Cmin. |
| **Protein Binding** | 60% |
| **Vd** | Widely distributed in the body. |
| **Tmax** | 0.8 hours |
| **serum T ½** | 1.8 hours |
| **Drug Concentrations** | With 800 mg q8h dosing, steady-state indinavir plasma concentrations were: Cmin 251 ± 178 nM, Cmax 12,617 ± 4037 nM, and AUC 30,691 ± 11,407 nM•hour.<br>In vivo intracellular accumulation: cell/plasma ratio 0.51-2.87 (indinavir alone), 4.87-7.45 when dosed with ritonavir.<br><br>Drug concentrations in pregnancy:<br>Dose of 800 mg TID yields suboptimal drug levels in pregnancy. In a kinetic study of 16 pregnant women, indinavir AUC was ↓ 74% compared to AUCs measured in post-partum women. Also, |

 

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| | 6/11 (55%) women in this kinetic study had undetectable indinavir Cmin at 8 hours post-dose. Therefore, indinavir use is NOT RECOMMENDED in HIV-infected pregnant women.<br><br>In a Thai cohort of HIV-infected pregnant women receiving indinavir 400/ritonavir 100 mg BID, median indinavir AUC during the 2nd and 3rd trimesters were ~40% lower compared to post-partum, and ~30% of pregnant women failed to achieve an indinavir Ctrough >0.1 ug/mL. Use of a higher indinavir dose may be necessary to ensure adequate exposure throughout pregnancy.[Cressey et al. 2012] |
| **Minimum target trough concentrations (for wildtype virus)** | 0.1 mg/mL |
| **CSF (% of serum)** | Some detected in animals. In series (n=25) of HIV-infected subjects taking combination therapy including indinavir, median CSF concentration was 210 nmol/L (>IC95 in vitro), suggesting that indinavir is present at therapeutic concentrations in CSF [Martin et al. 1999]<br><br>2010 CNS Penetration Effectiveness (CPE) Score: 4 (boosted indinavir), 3 (unboosted indinavir)<br>[Letendre S et al. 2010] |
| **Metabolism** | Metabolized- 7 metabolites.<br>CYP3A4 major enzyme involved in metabolism. Inhibits CYP3A4. May also be a weak inhibitor of CYP2D6. |
| **Excretion** | Primarily hepatically metabolized; 20% excreted unchanged in urine. |
| **Dosing – Adult** | **Unboosted dose:** 800mg po q8h<br>Food ↓ AUC by 78%. Take on an **empty stomach** with plenty of **liquid** (1.5L/day)- water, coffee, tea, skim milk ok.<br>-If nausea is a problem, take with a light meal low in protein and fat (ie. dry toast with jelly, corn flakes with skim milk and sugar).<br><br>**Boosted dose:** 800 mg po BID + ritonavir 100-200 mg BID<br>May take this combination with or without food, however food will help to minimize nausea. Fluid requirements of 1.5 L/day is still important. |
| **Dosing – Pediatric** | **Pediatric**[1]:<br>500 mg/m$^2$/dose po q8h<br>(Range: 300-500 mg/m$^2$/dose po q8h)<br><br>**Neonate**:<br>Do not give to neonates due to risk of hyperbilirubinemia |
| **Special instructions for pediatric patients** | Can open capsule and mix with water (but very unpalatable, tastes bitter); drink lots of water. NB: 10 mg/mL indinavir syrup complex compounding formulation. Stable for 14 days in refrigerator, store in glass bottle. (Hugen et al. Am J Health Syst Pharm 2000; 57(14):1332-9). |
| **Adjust in Liver Dysfunction** | Subjects with mild/moderate hepatic insufficiency and clinical evidence of cirrhosis show 60% ↑ AUC compared to healthy controls, and ↑ t1/2 to 2.8 hours.<br>Reduce indinavir to 600mg po q8h in mild-moderate hepatic failure due to cirrhosis. |

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| **Adjust in Renal Failure/Dialysis** | Dosage adjustment not required. Use normal dosage in dialysis, irrespective of hemodialysis schedule. |
| **Toxicity** | **Renal:** dose-related nephrolithiasis- flank pain, hematuria, or kidney stones (4%)- **HYDRATION IMPORTANT**; can also see elevated creatinine, sterile pyuria, interstitial nephritis, hydronephrosis or renal atrophy<br>**GI:** nausea, vomiting, diarrhea, abdominal pain, metallic taste<br>**Hepatic:** indirect hyperbilirubinemia (unconjugated) (10-15%), ↑ LFTs, exacerbation of chronic liver disease<br>**CNS:** headache, dizziness<br>**Derm:** rash, dry skin, cracked lips, ingrown nails, alopecia<br>**Other:** haemolytic anemia, thrombocytopenia<br>Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat malditribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis. |
| **Pregnancy & Lactation** | Pregnancy risk category C. Minimal placental passage, however theorectical risk of exacerbation of hyperbilirunemia in the neonate.<br>NB: Dose of 800 mg TID yields suboptimal drug levels; in a kinetic study in 16 pregnant women, indinavir AUC was ↓ 74% compared to AUCs measured in post-partum women. Also, 6/11 (55%) women in this kinetic study had undetectable indinavir Cmin at 8 hours post-dose. Therefore, indinavir use is NOT RECOMMENDED in HIV-infected pregnant women. Efficacy of ritonavir-boosted indinavir in this population is unknown. Consider use of other PIs in pregnancy (i.e. nelfinavir, saquinavir/ritonavir combination). |
| **Drug Interactions** | Indinavir is an inhibitor of CYP3A4.<br>See Separate Drug Interaction Table. |
| **Baseline Assessment** | Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), renal dysfunction, and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, Tbilirubin, glucose, fasting cholesterol profile, urinalysis. |
| **Routine Labs** | CBC/diff, LFTs, Tbilirubin, glucose, creatinine q 3 mos, urinalysis. 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 white capsule; DIN 02229161<br>400mg white capsule; DIN 02229196 |
| **Storage** | Store at room temperature in tightly sealed container (with moisture sensitive- desiccant). Capsules likely stable for a few days with no desiccant. |

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