

Selected Properties of Lopinavir/ritonavir

Other names	Kaletra®, ABT-378
Manufacturer	Abbott Canada
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 activity: in the presence of 50% human serum, mean EC50 of lopinavir against laboratory isolates ranged from 0.04-0.18 ug/mL.
Resistance - genotypic	<p>Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations):</p> <p>Major: V32I, I47V/A, V82A/F/T/S,</p> <p>Minor: L10F/I/R/V, K20M/R, L24I, L33F, M46I/L, I50V, F53L, I54V/L/A/M/T/S, L63P, A71V/T, G73S, I84V, L90M</p> <p>* Accumulation of ≥6 mutations is associated with reduced virologic response</p> <p><i>There are emerging data that specific mutations, most notably I47A (and possibly I47V) and V32I are associated with high-level resistance.</i></p>
Resistance - phenotypic	<p>Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/):</p> <p>54V, 82A, 90M: 20-fold ↑</p> <p>46L, 54V, 82A, 90M: 33-fold ↑</p> <p>46I, 54V, 82A, 90M : 142-fold ↑</p> <p>46L, 48V, 54V, 82A, 90M: 55-fold ↑</p> <p>46I, 54V, 82T, 84V, 90M: 75-fold ↑</p> <p>46L, 48V, 54T, 82A : 75-fold ↑</p>
Cross-Resistance	Varying degrees of cross-resistance with other PIs. showed greater ↓ susceptibility to lopinavir
Oral Bioavailability	Not established in humans.

Effect of Food	<p><u>Capsules/solution:</u> Administration with a moderate fat meal (500-682 kcal, 23-25% calories from fat) increases lopinavir AUC 48%, C_{max} 23%. Administration with a high fat meal (872 kcal, 56% calories from fat) increases lopinavir AUC 97%, C_{max} 43%. Take capsules or oral solution with food.</p> <p><u>Tablets:</u> Tablets may be taken with or without food. No clinically significant changes in C_{max} and AUC were observed following administration of Kaletra tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of KALETRA tablets with a moderate fat meal (500 – 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 26.9% and 17.6%, respectively. Relative to fasting, administration of KALETRA tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9%, but not C_{max}.</p>
Protein Binding	98-99% (alpha-1-acid glycoprotein and albumin)
Vd	
Tmax	4 hours
serum T ½	5-6 hours
Drug Concentrations	<p>C_{trough} 7.1 ± 2.9 ug/mL, C_{min} 5.5 ± 2.7 ug/mL, AUC 92.6 ± 36.7 ug.h/mL</p> <p>Body weight is a significant predictor of lopinavir kinetics (AUC, C_{max}); subjects with lower body weight tend to have higher lopinavir C_{max} and AUC [Bertz 2001]</p> <p>In vivo intracellular accumulation: cell/plasma ratio 0.65-1.55 when dosed with ritonavir.</p>
Minimum target trough concentrations (for wildtype virus)	4 mg/mL

CSF (% of serum)	<p>10 HIV infected adults taking LPV/RTV 400/100mg BID for > 4 weeks. Subjects were given their morning dose with a standardized breakfast. 8 plasma samples were drawn over a 12 hr period, 1 CSF sample was drawn</p> <ul style="list-style-type: none"> • Median LPV Plasma kinetics: AUC: 71.3 h.ug/ml, Cmin 3.82ug/ml, Cmax 9.38 ug/ml, Conc at 9hrs: 5.42 ug/ml • Median CSF kinetics (IQR): Conc at 9hrs: 11.2 ng/ml (6.76-16.4), • CSF: Plasma Ratio: 0.225% (0.194-0.324) <p>Authors state end of dosing interval LPV CSF concentrations were above the median IC₅₀ for <i>wt</i>HIV-1 for this dosing regimen [Dicenzo et al. ICAAC 2007].</p>
Metabolism	<p>CYP3A4 substrate; inhibits CYP3A4, 2D6 (to lesser extent). Induces glucuronyl transferases and possibly CYP1A2³, CYP2C19 and 2C9.⁴</p>
Excretion	<p>After multiple dosing, <3% lopinavir excreted unchanged in urine</p>
Dosing – Adult	<ul style="list-style-type: none"> • LPV 400 mg + RTV 100 mg po BID (3 capsules BID OR 2 tablets BID) • LPV 800 + RTV 200 mg once daily (6 capsules once daily OR 4 tablets once daily) approved in U.S. for naïve patients • With EFV or NVP <ul style="list-style-type: none"> ○ Treatment Naïve: LPV 400mg + RTV 100mg po BID (2 tablets BID) ○ Treatment Experienced: LPV 600mg + RTV 150mg po BID (3 tablets BID) ○ If Using Capsules: LPV 533 mg + RTV 133 mg po BID (4 capsules BID)

<p>Dosing – Pediatric</p>	<p>Neonates/Infants: no data for < 6 months old</p> <p>Pediatrics (6 months to 12 years of age): 7 to < 15 kg: LPV 12 mg/kg + RTV 3 mg/kg BID 15-40 kg: LPV 10 mg/kg + RTV 2.5 mg/kg BID > 40 kg: LPV 400 mg + RTV 100 mg po BID</p> <p>OR</p> <p>230/57.5 mg/m² BID with food, up to a maximum dose of 400/100 mg twice daily. Dosing guidelines based on body surface area available in Kaletra® product monograph.</p> <p><u>With efavirenz or nevirapine:</u> 7 to < 15 kg: LPV 13 mg/kg + RTV 3.25 mg/kg BID 15-50 kg: LPV 11 mg/kg + RTV 2.75 mg/kg BID > 50 kg: LPV 533 mg + RTV 133 mg BID</p> <p>OR</p> <p>300/75 mg/m² BID with food, up to a maximum dose of 533/133 mg twice daily.</p>
<p>Special instructions for pediatric patients</p>	<p>Administer doses with a calibrated oral dosing syringe.</p> <p>Propylene glycol content: capsules (64 mg), solution (153 mg/mL). During encapsulation process, exposure to soya protein lecithin and fractionated coconut oil occurs (?peanut allergy).</p> <p>Tablets should be swallowed whole and not chewed, broken, or crushed. Risk of tablets shattering if broken/crushed. Also in house animal data suggest reduced bioavailability if tablets are broken (personal communication, Abbott Laboratories, November 15, 2006).</p>
<p>Adjust in Liver Dysfunction</p>	<p>No dosage recommendation available, use with caution in hepatic impairment.</p>
<p>Adjust in Renal Failure/Dialysis</p>	<p>Dosage adjustment not necessary [Gupta et al. CROI 2006]. May administer drug regardless of hemodialysis schedule.</p>
<p>Toxicity</p>	<p>GI: abnormal stools, diarrhea, nausea, vomiting (higher incidence with QD dosing), abdominal pain, asthenia.</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 C. Limited experience in human pregnancy. When dosed at normal adult doses in pregnancy, lower than optimal drug concentrations may be seen. Higher doses may be required, though guidelines are not yet available. Monitor virologic response closely. Secreted into breast milk of lactating rats. Call 1-800-258-4263 to register patients in Antiretroviral Pregnancy Registry.
Drug Interactions	Lopinavir is a substrate and weak inhibitor of CYP3A4. Potential for interactions with other enzyme inducers or inhibitors [see also Interactions with Ritonavir]. See separate Drug Interaction Table for more information.
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	<p>Combination orange coloured soft-gel capsule (133.3 mg lopinavir/33.3 mg ritonavir); DIN 02243643. Capsules contain lecithin and coconut oil. In Canada, lopinavir/ritonavir capsules are exposed to soy lecithin. As peanut and soy are from the same plant family, some patients allergic to peanuts may also be allergic to soy (consult an allergist prior to taking capsules).</p> <p>Oral solution: 80mg/20 mg per mL solution; DIN 02243644. NB: oral solution contains 42.4% alcohol (v/v).</p> <p>Combination yellow film-coated tablet (200 mg lopinavir/50 mg ritonavir), 120 tablets/bottle; DIN 02285533. 100/25 mg tablet available in the U.S.</p>
Storage	<p>Capsules & Solution: Stable in refrigerator until expiry date. Stable at room temperature (< 25°C) for 2 months.</p> <p>Store film-coated tablets at 20°- 25°C; excursions permitted to 15°-30°C. Exposure of tablets to high humidity outside the original container for longer than 2 weeks is not recommended.</p>

References:

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