Selected Properties of Lopinavir/ritonavir

Other names	Kaletra®, ABT-378
Manufacturer	Abbott Laboratories, Ltd.
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	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: V32I, I47V/A, V82A/F/T/S, 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 *Accumulation of ≥6 mutations is associated with reduced virologic response *There are emerging data that specific mutations, most notably I47A (and possibly I47V) and V32I are associated with high-level resistance.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): 54V, 82A, 90M: 20-fold ↑ 46L, 54V, 82A, 90M: 33-fold ↑ 46I, 54V, 82A, 90M : 142-fold ↑ 46L, 48V, 54V, 82A, 90M: 55-fold ↑ 46I, 54V, 82T, 84V, 90M: 75-fold ↑ 46L, 48V, 54T, 82A : 75-fold ↑
Cross-Resistance	Varying degrees of cross-resistance with other PIs showed greater ↓ susceptibility to lopinavir
Oral Bioavailability	Not established in humans.
Effect of Food	Capsules/solution: Administration with a moderate fat meal (500-682 kcal, 23-25% calories from fat) increases lopinavir AUC 48%, Cmax 23%. Administration with a high fat meal (872 kcal, 56% calories from fat) increases lopinavir AUC 97%, Cmax 43%. Take capsules or oral solution with food. Tablets: 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

<table>
<tr><td></td><td>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}.</td></tr>
<tr><td>Protein Binding</td><td>98-99% (alpha-1-acid glycoprotein and albumin)</td></tr>
<tr><td>Vd</td><td></td></tr>
<tr><td>Tmax</td><td>4 hours</td></tr>
<tr><td>serum T ½</td><td>5-6 hours</td></tr>
<tr><td>Drug Concentrations</td><td>Ctrough 7.1 ± 2.9 ug/mL, Cmin 5.5 ± 2.7 ug/mL, AUC 92.6 ± 36.7 ug.h/mL
Body weight is a significant predictor of lopinavir kinetics (AUC, Cmax); subjects with lower body weight tend to have higher lopinavir Cmax and AUC [Bertz 2001]
In vivo intracellular accumulation: cell/plasma ratio 0.65-1.55 when dosed with ritonavir.

23 Thai HIV infected children (age 2-18 years) were randomized to standard dose of LPV (according to WHO dosing table) or low dose of LPV (70% of recommended dose); NRTI backbone was AZT + 3TC, kinetic study done at 4-6 weeks.
<table>
<tr><td></td><td>LPV/r standard dose
N = 11</td><td>LPV/r low dose
N =12</td></tr>
<tr><td>Median dose</td><td>288 mg/m2 BID</td><td>194 mg/m2 BID</td></tr>
<tr><td>Mean AUC 0-12hr</td><td>107.1 h.mg/L</td><td>84.6 h.mg/L</td></tr>
<tr><td>Mean Cmax</td><td>11.9 mg/L</td><td>9.8 mg/L</td></tr>
<tr><td>Mean Cmin</td><td>5.2 mg/L</td><td>3.8 mg/L</td></tr>
</table>
1 child in low dose group had subtherapeutic LPV/r concentration (< 1mg/L). There was no statistical difference in CD4 and VL between the groups (van Der Lugt et al. 2008).

Comparison of lopinavir and ritonavir tablet and soft gelatin capsule (SGC) pharmacokinetics in anti-retroviral naive HIV-1 infected subjects:
LPV 400mg/100mg BID: Tab formulation: LPV conc ↑ 14-25% VS SGC;
LPV/r 800mg/200mg OD: Tab formulation: LPV conc ↑19-38% VS SGC [Klein et al. 2008]

Fixed-dose combination tablets of lopinavir/ritonavir/lamivudine or lopinavir/ritonavir/lamivudine/zidovudine shown to be bioequivalent to the individual marketed products under fasting conditions. The food effect on both fixed-dose combinations is similar to that of the marketed products.[Salem et al. 2014</td></tr>
</table>

	IWCPHT]
Minimum target trough concentrations (for wildtype virus)	4 mg/mL
CSF (% of serum)	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 • 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)** Authors state end of dosing interval LPV CSF concentrations were above the median IC_{50} for *wt*HIV-1 for this dosing regimen [Dicenzo et al. 2009]. 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	CYP3A4 substrate; inhibits CYP3A4, 2D6 (to lesser extent). Induces glucuronyl transferases and possibly CYP1A2[3], CYP2C19 and 2C9.[4]
Excretion	After multiple dosing, <3% lopinavir excreted unchanged in urine

Dosing – Adult	• Lopinavir 400 mg/ritonavir 100 mg po BID (2 tablets BID)
	• Lopinavir 800 mg/ritonavir 200 mg once daily (4 tablets once daily) in patients with less than 3 mutations associated with lopinavir resistance. Once-daily dosing is NOT recommended in:
	  ○ Patients with ≥3 of the following mutations: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V
	  ○ Pediatric patients
	  ○ Pregnant patient
	• .
	• With efavirenz or nevirapine:
	  ○ Treatment Naïve: LPV 400mg + RTV 100mg po BID (2 tablets BID)
	  ○ Treatment Experienced: LPV 600mg + RTV 150mg po BID (3 tablets BID)

Dosing – Pediatric	Kaletra oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). KALETRA oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events.

	Pediatrics (6 months to 18 years of age): Dose based on weight or body surface area. Pediatric dosing guidelines for oral solution and tablets based on weight: **Weight (kg) / Twice Daily Dose (mg/kg)* / Volume of Oral Solution Twice Daily (80 mg lopinavir/20 mg ritonavir per mL)† / Number of 100/25 mg Tablets Twice Daily‡** 7 to < 15 kg — 12 mg/kg — Tablets are not recommended. Use oral solution. 7 to 10 kg — 1.25 mL > 10 to < 15 kg — 1.75 mL 15 to 40 kg — 10 mg/kg 15 to 20 kg — 2.25 mL — 2 > 20 to 25 kg — 2.75 mL — 2 > 25 to 30 kg — 3.50 mL — 3 > 30 to 35 kg — 4.00 mL — 3 > 35 to 40 kg — 4.75 mL — 4 (or two 200/50 mg tablets) > 40 kg — See adult dosage recommendation * Dosing based on the lopinavir component of KALETRA® oral solution (80 mg/20 mg per mL). † KALETRA® oral solution should be taken with food. ‡ KALETRA® tablets may be taken with or without food. Refer to Kaletra product monograph for further details if dosing by body surface area or with concomitant NNRTIs, nelfinavir or amprenavir.
Special instructions for pediatric patients	Administer doses with a calibrated oral dosing syringe. Kaletra oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. Kaletra oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Postmarketing life-threatening cases of cardiac toxicity, lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving Kaletra oral solution. Tablets should be swallowed whole and not chewed, broken, or crushed. Risk of tablets shattering if broken/crushed. Administration of crushed 200/50 mg lopinavir/ritonavir tablets to children significantly reduced lopinavir and ritonavir exposure with a decrease in AUC by 45% and 47%, respectively. Therefore, the use of crushed lopinavir/ritonavir tablets should be avoided, if possible.[Best et al. JAIDS 2011;58:385-91]
Adjust in Liver Dysfunction	No dosage recommendation available, use with caution in hepatic impairment. Steady-state 12-hour lopinavir/ritonavir pharmacokinetic profiles were assessed in 15 HIV-positive patients coinfected with HCV/HBV (Child-Pugh class A) taking 400/100 mg BID; data were compared to an HIV-positive cohort without hepatitis.

	Lopinavir pharmacokinetics were not altered in the presence of chronic HBV/HCV coinfection compared to the cohort without hepatitis.[von Hentig et al. 2010].
Adjust in Renal Failure/Dialysis	In a prospective study of HIV-infected patients on hemodialysis taking lopinavir/ritonavir capsules 400/100 mg BID (n=13), 12-hour PK was assessed. Mean Cmin, Cmax, and AUC were 2.76 mg/mL, 8.45 mg/mL and 69.6mg h/mL for lopinavir and 0.08mg/mL, 0.58mg/mL and 3.74mg h/mL for ritonavir. The AUC geometric mean ratios (90% CI) for LPV and RTV were 81% (67, 97), and 92% (76, 111), respectively. LPV Cmin was lower than expected in the hemodialysis group. No dosing adjustments are required in treatment-naïve patients. May wish to consider TDM in treatment-experienced patients. May administer drug regardless of hemodialysis schedule. [Gupta et al. 2008]
Toxicity	**GI**: abnormal stools, diarrhea, nausea, vomiting (higher incidence with QD dosing), abdominal pain, asthenia. **Other:** Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.

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. In a prospective, nonblinded, pharmacokinetic study in HIV-infected pregnant women, 33 subjects received 2 lopinavir tablets (400/100 mg) BID during the 2nd trimester, 3 tablets (600/150 mg) BID in the 3rd trimester, and 2 tablets (400/100 mg) BID post-delivery through 2 weeks postpartum. Median lopinavir AUC was 72, 96 and 133 ug.hr/mL and median lopinavir Cmin was 3.4, 4.9 and 6.9 ug/mL in the 2nd trimester, 3rd trimester and postpartum, respectively. Recommend using higher lopinavir dose in 2nd and 3rd trimesters of pregnancy to achieve exposures similar to those in non-pregnant subjects taking standard LPVr. May reduce to standard lopinavir dosing postpartum.[Best et al. 2010]. In a prospective longitudinal PK study of 12 HIV-infected women on lopinavir/r 400/100 mg BID who underwent intensive PK evaluations of total (protein-bound and unbound) and unbound lopinavir/r during and after pregnancy, total LPV AUC was significantly lower than postpartum AUC (p=0.005), but unbound LPV AUC and C12h remained unchanged during pregnancy despite a 25% dose increase in the last trimester. These findings suggest that dose adjustments may not be required in all HIV-infected pregnant women.[Patterson et al. 2013] Secreted into breast milk of lactating rats. Call 1-800-258-4263 to register patients in Antiretroviral Pregnancy Registry. In 23 HIV-infected pregnant women receiving lopinavir/ritonavir (all VL<40 copies/mL at delivery), mean lopinavir cord blood concentration was 369.3 ng/mL (78.2% were below cut-off values). Mean amniotic fluid:maternal plasma ratio for lopinavir was 0.06. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010].
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	Oral solution: 80mg/20 mg per mL solution; DIN 02243644. NB: oral solution contains 42.4% alcohol (v/v) and 15.3% (w/v) propylene glycol.

	Combination yellow film-coated tablet (200 mg lopinavir/50 mg ritonavir), 120 tablets/bottle; DIN 02285533. 100/25 mg pale yellow film-coated tablet, 60 tablets/bottle, DIN 02312301. Fixed-dose combination tablets of lopinavir/ritonavir/lamivudine or lopinavir/ritonavir/lamivudine/zidovudine are under development. NB: soft-gel capsules were discontinued in July 2008. 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). Propylene glycol content: capsules (64 mg), solution (153 mg/mL).
Storage	Solution: Stable in refrigerator until expiry date. Stable at room temperature (< 25°C) for 2 months. 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.

References:

Abbott Laboratories Ltd. Kaletra® Product Monograph. St-Laurent, QC. December 9th, 2011.

Bertz R et al. Effects of gender, race, age and weight on the pharmacokinetics of lopinavir after single-dose Kaletra in healthy adult populations [abstract 3.11]. 2nd International Workshop on HIV Pharmacology. Noordwijk, the Netherlands. April 2-4, 2001.

Best BM, Capparelli EV, Diep H, Rossi SS, Farrell MJ, Williams E, Lee G et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. JAIDS 2011;58:385-91.

Best BM, Stek AM, Mirochnick M, Hu C, Li H, Burchett SK, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. JAIDS 2010;54(4):381-8.

Dicenzo R, Difrancesco R, Cruttenden K, Donnelly J, Schifitto G. Lopinavir cerebrospinal fluid trough concentrations in HIV-infected adults. Ann Pharmacother 2009;43[epub ahead of print].

Ford J, Khoo SH, Back DJ. The intracellular pharmacology of antiretroviral protease inhibitors. JAC 2004 (advance on-line publication).

Gupta S, Rosenkranz S, Cramer Y, Koletar S, et al. The pharmacokinetics and pharmacogenomics of efavirenz and lopinavir/ritonavir in HIV-infected persons requiring hemodialysis. AIDS 2008;22:1919–1927.

Ivanovic J, Nicastri E, Viscione M, Bellagamba R, Signore F, Pisani G et al. Cord blood and amniotic fluid exposures of protease inhibitors and viral load quantification in HIV-infected pregnant women [abstract

WEPE0100]. XVIII International AIDS Conference, Vienna, Austria, July 18-23rd, 2010.

Klein C et al. Comparison of lopinavir and ritonavir tablet and soft gelatin capsule (SGC) pharmacokinetics in anti-retroviral naive HIV-1 infected subjects [abstractc P37]. 9th International Workshop on Clinical Pharmacology of HIV Therapy. New Orleans, USA, April 7-9, 2008.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Patterson KB, Dumond JB, Prince HA, Jenkins AJ, Scarsi KK, Wang R et al. Protein binding of lopinavir and ritonavir during 4 phases of pregnancy: implications for treatment guidelines. JAIDS 2013;63:51-8.

Salem AH, Chiu YL, Valdes JM et al. Lopinavir/ritonavir/lamivudine as a fixed-dose combination tablet: assessment of bioequivalence and effect of food on bioavailability [abstract P_03]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, Washington DC, May 19-22, 2014.

Salem AH, Chiu YL, Valdes JM et al. Assessment of bioequivalence and food effect for a complete antiretroviral fixed-dose combination of lopinavir, ritonavir, lamivudine and zidovudine [abstract P_04]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, Washington DC, May 19-22, 2014.

Van der Lugt J, Puthanakit T, Gorowara M, Bunupuradah T, Butterworth O, Phasomsap C, et al. Low-dose lopinavir/ritonavir provides adequate plasma concentrations in Thai HIV infected children [abstract P16]. 9th International Workshop on Clinical Pharmacology of HIV Therapy. New Orleans, USA, April 7-9, 2008.

Von Hentig N, Khaykin P, Stephan C, Nisius G, Bickel M, Haberl A et al. Hepatitis/HIV co-infection without hepatic impairment does not alter lopinavir plasma concentrations in HIV-1 infected adults [abstract 57]. 11th International Workshop on HIV Pharmacology, Sorrento, Italy, April 5-7, 2010.

Yeh R, Gaver V, Patterson K, Rezk N, Baxter-Meheux F, Blake MJ, et al. Lopinavir/ritonavir induces the hepatic activity of cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP1A2 but inhibits the hepatic and intestinal activity of CYP3A as measured by a phenotyping drug cocktail in healthy volunteers. J Acquir Immune Defic Syndr 2006;42:52-60.

