

DATA SHEET

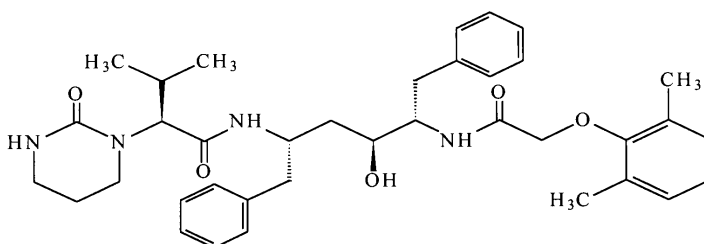
KALETRA® TABLETS AND ORAL SOLUTION

NAME OF THE MEDICINE

Lopinavir / ritonavir

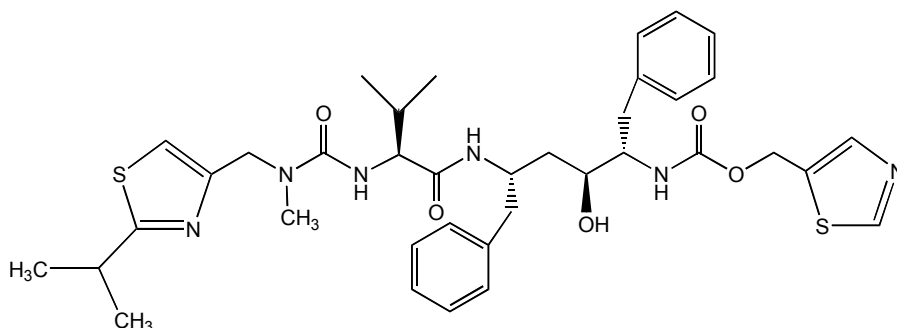
Chemical Structure

Lopinavir is chemically designated as [1S-[1R*,(R*), 3R*, 4R*]]-N-[4-[[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir has the following structural formula:



Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

Ritonavir is chemically designated as 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir has the following structural formula:



Ritonavir is a white to light tan powder. Ritonavir has a bitter metallic taste. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water.

CAS Numbers

Lopinavir: 192725-17-0

Ritonavir: 155214-67-5

DESCRIPTION

Kaletra is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. As co-formulated in Kaletra, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Kaletra tablets are available for oral administration in a strength of 200 mg of lopinavir and 50 mg of ritonavir with the following inactive ingredients: copovidone, sorbitan monolaurate, silica-colloidal anhydrous, and sodium stearyl fumarate and the following inactive ingredients in the film coating: hypromellose, titanium dioxide, macrogol 400, hydroxypropylcellulose, talc, silica-colloidal anhydrous, macrogol 3350, iron oxide yellow CI 77492, and polysorbate 80.

Kaletra tablets are also available in a strength of 100 mg of lopinavir and 25 mg of ritonavir with the following inactive ingredients: copovidone, sorbitan monolaurate, silica-colloidal anhydrous, and sodium stearyl fumarate and the following inactive ingredients in the film coating: polyvinyl alcohol, titanium dioxide, talc, macrogol 3350, iron oxide yellow CI 77492.

Kaletra Oral Solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per millilitre with the following ingredients: PEG-40 hydrogenated castor oil, purified water, sodium chloride, sodium citrate, saccharin sodium, acesulfame potassium, anhydrous citric acid, absolute ethanol, propylene glycol, menthol, povidone, glycerol, high fructose maize syrup, peppermint oil, water, Magnasweet Flavour (2x) (ARTG No. 4333), Vanilla natural & artificial flavour (Yarnilla) 33869 (ARTG No. 4338) and Artificial cotton candy flavour (ARTG No. 4381).

Kaletra Oral Solution contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v)

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Lopinavir, an inhibitor of the HIV-1 and HIV-2 proteases, prevents cleavage of the gag-pol polyprotein, resulting in the production of immature, non-infectious virus.

Antiviral activity in-vitro

The in-vitro antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC₅₀) of lopinavir against five different HIV-1 laboratory strains ranged from 10 to 27 nM (0.006 to 0.017 mcg/mL, 1 mcg/mL equals 1.6 microM) and ranged from 4 to 11 nM (0.003 to 0.007 mcg/mL) against several HIV-1 clinical isolates (n=6). In the presence of 50% human serum, the mean EC₅₀ of lopinavir against these five laboratory strains ranged from 65 to 289 nM (0.04 to 0.18 mcg/mL), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected in-vitro. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses in-vitro.

The selection of resistance to Kaletra in antiretroviral treatment naive patients has not yet been characterized. In a Phase III study of 653 antiretroviral treatment naive patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV greater than 400 copies/mL at week 24, 32, 40 and/or 48 were analyzed. No evidence of genotypic or phenotypic resistance to Kaletra was observed in 37 evaluable Kaletra-treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV

protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to Kaletra in antiretroviral treatment naive paediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

Resistance to Kaletra has been noted to emerge in patients treated with other protease inhibitors prior to Kaletra therapy. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (greater than 400 copies/mL) viral RNA following treatment with Kaletra for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least four mutations associated with protease inhibitor resistance immediately prior to Kaletra therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on Kaletra therapy. The assessment of these mutational patterns is under study.

Cross-Resistance During Kaletra Therapy

Little information is available on the cross-resistance of viruses selected during therapy with Kaletra. Isolates from four patients previously treated with one or more protease inhibitors that developed increased lopinavir phenotypic resistance during Kaletra therapy either remained cross-resistant or developed cross-resistance to ritonavir, indinavir, and nelfinavir. All rebound viruses either remained fully sensitive or demonstrated modestly reduced susceptibility to amprenavir (up to 8.5-fold concurrent with 99-fold resistance to lopinavir). The rebound isolates from the two subjects with no prior saquinavir treatment remained fully sensitive to saquinavir.

Genotypic correlates of reduced virologic response in antiretroviral-experienced patients initiating a Kaletra-based combination regimen

Baseline mutations at codons L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/F/T, and I84V in HIV protease were found to be correlated with reduced virologic response to lopinavir. In lopinavir/ritonavir clinical database, the presence of protease mutations at positions 10, 20, 33, 36, 54 and 82 in the presence of multiple other protease mutations was statistically significantly associated with a lowered virologic response (HIV-1 RNA < 400 copies/mL within 12 months after administration of lopinavir/ritonavir) by logistic regression analysis. The presence of mutations at codons 47, 48 and 50 are also appeared to influence response, although the association was not statistically significant. Table 1 shows the 48-week virologic response (HIV RNA <400 copies/mL) according to the number of the above protease inhibitor resistance mutations at baseline in studies M98-888 and M97-765 and study M98-957 (see below).

Table 1: Virologic Response (HIV RNA <400 copies/mL) at Week 48 by Baseline Kaletra Susceptibility and by Number of Protease Substitutions Associated with Reduced Response to Kaletra¹			
No. of subjects with virologic response / total no. of subjects (%)			
Number of protease inhibitor mutations at baseline ¹	Study M98-888 (Single protease inhibitor-experienced ² , NNRTI-naïve) n = 130	Study M97-765 (Single protease inhibitor-experienced ³ , NNRTI-naïve) n = 56	Study M98-957 (Multiple protease inhibitor-experienced ⁴ , NNRTI-naïve) n = 50
0-2	76/103 (74%)	34/45 (76%)	19/20 (95%)

3-5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	n/a	1/4 (25%)
¹ Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L241, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V ² 43% indinavir, 42% nelfinavir, 10% ritonavir, 15% saquinavir ³ 41% indinavir, 38% nelfinavir, 4% ritonavir, 16% saquinavir ⁴ 86% indinavir, 54% nelfinavir, 80% ritonavir, 70% saquinavir			

Table 2 shows the 48-week virologic response (HIV-1 RNA <50 copies/mL) in study 802 according to the number of lopinavir-associated resistance mutations listed in Table 1 present at baseline (see Clinical Studies). There are insufficient data to support once daily administration of Kaletra for adult patients with three or more lopinavir-associated mutations.

Table 2: Virologic Response (HIV-1 RNA <50 copies/mL) at Week 48 by Baseline Number of Protease Substitutions Associated with Reduced Response to Kaletra¹		
Number of protease inhibitor substitutions at baseline ¹	Study 802 (Treatment experienced ²) Kaletra Once Daily + NRTIs n=268	Study 802 (Treatment experienced ³) Kaletra Twice Daily + NRTIs n=264
0-2	167/255 (65%)	154/250 (62%)
3-5	4/13 (31%)	8/14 (57%)
6 or more	N/A	N/A
¹ Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. ² 88% NNRTI-experienced, 47% PI-experienced (24% nelfinavir, 19% indinavir, 13% atazanavir). ³ 81% NNRTI-experienced, 45% PI-experienced (20% nelfinavir, 17% indinavir, 13% atazanavir).		

Clinical Studies

Antiviral Activity of Kaletra in Patients With Previous Protease Inhibitor Therapy

The clinical relevance of reduced in-vitro susceptibility to lopinavir has been examined by assessing the virologic response to Kaletra therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naive patients with HIV RNA greater than 1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir, and ritonavir (Study M98-957). In this study, patients were initially randomised to receive one of two doses of Kaletra in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC50 values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC50 against wild-type HIV. Fifty-five percent (31/56) of these baseline isolates displayed a greater than 4-fold reduced susceptibility to lopinavir. These 31 isolates had a mean reduction in lopinavir susceptibility of 27.9-fold.

After 48 weeks of treatment with Kaletra, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA less than or equal to 400 copies/mL was observed in 93% (25/27), 73% (11/15), and 25% (2/8) of patients with less than or equal to 10-fold, greater than 10 and less than 40-fold, and greater than or equal to 40-fold reduced susceptibility to lopinavir at baseline, respectively. Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic. Plasma HIV RNA less than or equal to

50 copies/mL was observed in 81% (22/27), 60% (9/15), and 25% (2/8) in the above groups of patients, respectively.

There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on Kaletra therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

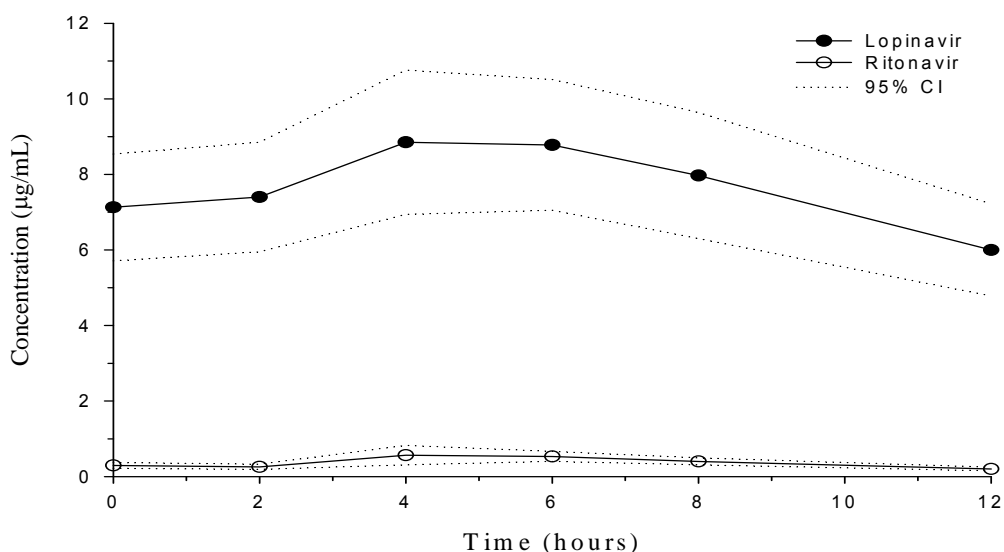
Pharmacokinetics

The pharmacokinetic properties of lopinavir coadministered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolised by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir.

Across studies, administration of Kaletra 400/100 mg BD yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg BD. The in-vitro antiviral EC₅₀ of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of Kaletra is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after Kaletra 400/100 mg BD with food for three weeks from a pharmacokinetic study in HIV-infected adult subjects (n=19).

Figure 1: Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (n = 19)



Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg tablets are equal to or greater than those obtained with three 133/33 mg capsules under fed conditions with less pharmacokinetic variability.

Absorption

Multiple dosing with 400/100 mg Kaletra tablets twice daily for 2 weeks and without meal restriction produced a mean \pm SD lopinavir peak plasma concentration (C_{max}) of 12.3 ± 5.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged

113.2 ± 60.5 µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of Food on Oral Absorption

Administration of a single 400/100 mg dose of Kaletra tablets under fed conditions (high-fat, 872 kcal, 56% from fat) compared to the fasted state was associated with no significant changes in C_{max} and AUC_{inf} , therefore, Kaletra tablets may be taken with or without food. Kaletra tablets have also shown less pharmacokinetic variability under all meal conditions compared to the Kaletra capsule.

Administration of Kaletra Oral Solution under nonfasting conditions, with a moderate fat meal (500-682 kcal, 22.7 to 25.1% calories from fat), lead to the mean increases of lopinavir AUC and C_{max} to 80 and 54% respectively. Relative to fasting, administration of Kaletra Oral Solution with a high fat meal (872kcal, 55.8% from fat), increased lopinavir AUC and C_{max} by 130 and 56% respectively.

To enhance bioavailability and minimize pharmacokinetic variability, Kaletra Oral Solution should be taken with food.

Distribution

At steady state, lopinavir is approximately 98 to 99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin, however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg Kaletra BD, and is similar between healthy volunteers and HIV-positive patients.

Metabolism

In-vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor, which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C -lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg Kaletra dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination

Following a 400/100 mg ^{14}C -lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C -lopinavir can be accounted for in urine and feces, respectively, after eight days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5.98 ± 5.75 L/hr (mean ± SD, n=19).

Once Daily Dosing

The pharmacokinetics of once daily Kaletra tablets have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. Kaletra 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once daily regimen. Multiple dosing of 800/200 mg Kaletra once daily for 2 weeks without meal restriction (n=16) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 14.8 ± 3.5 µg/ml, occurring approximately 6 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 5.4 µg/ml. Lopinavir AUC over a 24 hour dosing interval averaged 206.5 ± 89.7 µg•h/ml.

Effects on Electrocardiogram

QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once-daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) differences in QTcF from placebo were 3.6 (6.3) msec and 13.1(15.8) msec for 400/100 mg twice-daily and supratherapeutic 800/200 mg twice-daily lopinavir/ritonavir, respectively. The two regimens resulted in exposures on Day 3 that were approximately 1.5 and 3-fold higher than those observed with recommended once-daily or twice-daily lopinavir/ritonavir doses at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Modest prolongation of the PR interval was also noted in subjects receiving lopinavir/ritonavir in the same study on Day 3. Maximum PR interval was 286 msec and no second or third degree heart block was observed (see PRECAUTIONS).

Special Populations

Gender, Race and Age:

Lopinavir pharmacokinetics have not been studied in elderly patients. No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified.

Paediatric Patients

The pharmacokinetics of Kaletra 300/75 mg/m² BD and 230/57.5 mg/m² BD have been studied in a total of 53 paediatric patients, ranging in age from six months to 12 years. The 230/57.5 mg/m² BD regimen without nevirapine and the 300/75 mg/m² BD regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BD regimen (without nevirapine).

The lopinavir mean steady-state AUC, C_{max}, and C_{min} were 72.6 \pm 31.1 mcg·h/mL, 8.2 \pm 2.9 and 3.4 \pm 2.1 mcg/mL, respectively after Kaletra 230/57.5 mg/m² BD without nevirapine (n=12), and were 85.8 \pm 36.9 mcg·h/mL, 10.0 \pm 3.3 and 3.6 \pm 3.5 mcg/mL, respectively after 300/75 mg/m² BD with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BD (six months to eight years) or 4 mg/kg BD (greater than eight years). Kaletra once daily has not been evaluated in paediatric patients.

Renal Impairment

Lopinavir pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Impairment

Lopinavir is principally metabolised and eliminated by the liver. Multiple dosing of lopinavir/ritonavir 400/100 mg twice daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV-infected subjects with normal hepatic function. Additionally, the plasma protein binding of lopinavir was lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31% respectively). Kaletra has not been studied in patients with severe hepatic impairment (see PRECAUTIONS – Hepatic Impairment).

Drug-Drug Interactions

(See also CONTRAINDICATIONS and PRECAUTIONS – Interactions with Other Medicines)

Kaletra is an inhibitor of the P450 isoform CYP3A in-vitro. Coadministration of Kaletra and drugs primarily metabolised by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see CONTRAINDICATIONS).

Kaletra does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

Kaletra has been shown in-vivo to induce its own metabolism and to increase the biotransformation of some drugs metabolised by cytochrome P450 enzymes and by glucuronidation.

Kaletra is metabolised by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, coadministration of Kaletra and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with Kaletra and other drugs likely to be coadministered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration of Kaletra on the AUC, C_{max} and C_{min} are summarized in Table 3 (effect of other drugs on lopinavir) and Table 4 (effect of Kaletra on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see PRECAUTIONS - Interactions with Other Medicines.

Table 3: Drug Interactions Pharmacokinetic Parameters for Lopinavir in the Presence of the Coadministered Drug (See PRECAUTIONS for Recommended Alterations in Dose or Regimen)						
Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Kaletra (mg)	n	Ratio (with/without coadministered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	750 BD; 10 days	400/100 capsule BD; 21 days	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin	20 Daily; 4 days	400/100 capsule BD; 14 days	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz ¹	600 nocte; 9 days	400/100 capsule BD; 9 days	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 nocte; 9 days	500/125 tablet BD 10 days	19	1.12 (1.02 – 1.23)	1.06 (0.96 – 1.17)	0.9 (0.78 – 1.04)
	600 nocte; 9 days	600/150 tablet BD; 10 days	23	1.36 (1.28 - 1.44)	1.36 (1.28 - 1.44)	1.32 (1.21 - 1.44)
Ketoconazole	200 single dose	400/100 capsule BD; 16 days	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 BD, 10 days	400/100 capsule BD; 21 days	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 BD, steady-state (>1yr) ²	400/100 capsule BD, steady-state (>1yr)	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg Daily, 2 weeks; BD 1 week ³	300/75 mg/m ² oral solution BD; 3 weeks	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)

Table 3: Drug Interactions Pharmacokinetic Parameters for Lopinavir in the Presence of the Coadministered Drug (See PRECAUTIONS for Recommended Alterations in Dose or Regimen)																		
Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Kaletra (mg)	n	Ratio (with/without coadministered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00														
				C _{max}	AUC	C _{min}												
Omeprazole	40 Daily, 5 days	400/100 tablet BD; 10 days	11	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)												
		800/200 tablet Daily; 10 days	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)												
Pravastatin	20 Daily; 4 days	400/100 capsule BD; 14 days	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)												
Ranitidine	150 single dose	400/100 tablet BD; 10 days	12	0.98 (0.95, 1.02)	0.98 (0.94, 1.01)	0.93 (0.89, 0.98)												
		800/200 tablet Daily; 10 days	11	0.97 (0.95, 1.00)	0.95 (0.91, 0.99)	0.82 (0.74, 0.91)												
Rifabutin	150 Daily; 10 days	400/100 capsule BD; 20 days	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)												
Rifampicin	600 Daily, 10 days	400/100 capsule BD; 20 days	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)												
							600 Daily, 14 days	800/200 capsule BD; 9 days ⁴	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)						
													600 Daily, 14 days	400/400 capsule BD; 9 days ⁵	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
Ritonavir ²	100 BD; 3 to 4 weeks	400/100 capsule BD; 3 to 4 weeks	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)												

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

¹ The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

² Study conducted in HIV-positive adult subjects.

³ Study conducted in HIV-positive paediatric subjects ranging in age from 6 months to 12 years.

⁴ Titrated to 800/200 BD as 533/133 BD x 1 day, 667/167 BD x 1 day, then 800/200 BD x 7 days, compared to 400/100 BD x 10 days alone.

⁵ Titrated to 400/400 BD as 400/200 BD x 1 day, 400/300 BD x 1 day, then 400/400 BD x 7 days, compared to 400/100 BD x 10 days alone.

* Parallel group design; n for Kaletra + coadministered drug, n for Kaletra alone

Table 4: Drug Interactions Pharmacokinetic Parameters for Coadministered Drug in the Presence of Kaletra (See PRECAUTIONS for Recommended Alterations in Dose or Regimen)						
Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Kaletra (mg)	n	Ratio (with/without Kaletra) of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C _{max}	AUC	C _{min}
Amprenavir ¹	750 BD, 10 days combo vs. 1200 BD, 14 days alone	400/100 capsule BD, 21 days	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Atorvastatin	20 Daily; 4 days	400/100 capsule BD; 14 days	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Desipramine ²	100 single dose	400/100 capsule BD; 10 days	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	NA
Efavirenz	600 nocte; 9 days	400/100 capsule BD; 9 days	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Oestradiol	35 mcg Daily; 21 days (Brevinor-1®)	400/100 capsule BD; 14 days	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir ¹	600 BD, 10 days combo nonfasting vs. 800 TDS, 5 days alone fasting	400/100 capsule BD, 15 days	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 capsule BD; 16 days	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	NA
Methadone	5 single dose	400/100 capsule BD; 10 days	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	NA
Nelfinavir ¹	1000 BD, 10 days combo vs. 1250 BD, 14 days alone	400/100 capsule BD, 21 days	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)
M8 metabolite				2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)
Nevirapine	200 Daily, 14 days; BD, 6 days	400/100 capsule BD; 20 days	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethisterone	1 Daily, 21 days (Brevinor-1®)	400/100 capsule BD; 14 days	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 Daily; 4 days	400/100 capsule BD; 14 days	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	NA
Rifabutin	150 Daily 10 days combo vs. 300 Daily, 10 days; alone	400/100 capsule BD, 10 days	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-O-desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)

Table 4: Drug Interactions Pharmacokinetic Parameters for Coadministered Drug in the Presence of Kaletra (See PRECAUTIONS for Recommended Alterations in Dose or Regimen)						
Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of Kaletra (mg)	n	Ratio (with/without Kaletra) of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C _{max}	AUC	C _{min}
Rifabutin + 25-O-desacetyl rifabutin ³				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Saquinavir ¹	800 BD, 10 days combo vs. 1200 TDS, 5 days alone,	400/100 capsule BD, 15 days 400/100 capsule BD, 20 days	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
	1200 BD, 5 days combo vs. 1200 TDS 5 days alone		10	6.44 (5.59, 7.41)	9.91 (8.28, 11.86)	16.54 (10.91, 25.08)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

¹ Ratio of parameters for amprenavir, indinavir, nelfinavir, and saquinavir are not normalized for dose.

² Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.

³ Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.

* Parallel group design; n for Kaletra + coadministered drug, n for coadministered drug alone.

NA = not available.

CLINICAL TRIALS

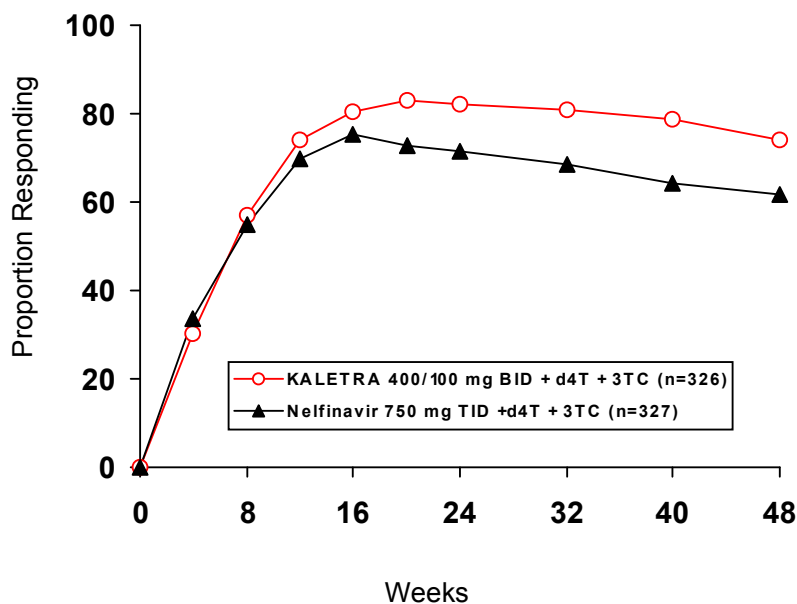
Patients Without Prior Antiretroviral Therapy

Study M98-863: Kaletra capsules BD + stavudine + lamivudine compared to nelfinavir TDS + stavudine + lamivudine.

Study M98-863 was a randomised, double-blind, multicentre trial comparing treatment with Kaletra capsules (400/100 mg BD) plus stavudine and lamivudine versus nelfinavir (750 mg TDS) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4 cell count was 259 cells/mm³ (range: 2 to 949 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.9 log₁₀ copies/mL (range: 2.6 to 6.8 log₁₀ copies/mL).

Treatment response and outcomes of randomised treatment are presented in Figure 2 and Table 5, respectively.

Figure 2: Treatment Response Through 48 Weeks* (Study 863)



* Proportion of patients at each time point who have achieved and maintained HIV RNA less than 400 copies/mL, are on their original study medication, and have not experienced a new CDC Class C event.

Outcome	Kaletra+d4T+3TC (n=326)	Nelfinavir+d4T+3TC (n=327)
Responder ^{*1}	75%	62%
Virologic failure ²	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse event	4%	4%
Discontinued for other reasons ³	10%	8%

^{*} Corresponds to rates at Week 48 in Figure 2.

¹ Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

² Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.

³ Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through week 48, including patients who discontinued subsequent to virologic failure, was 17% in the Kaletra arm and 24% in the nelfinavir arm.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the Kaletra arm compared to the nelfinavir arm with HIV RNA less than 400 copies/mL (75% vs. 62%, respectively) and HIV RNA less than 50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV RNA level subgroups is presented in Table 6.

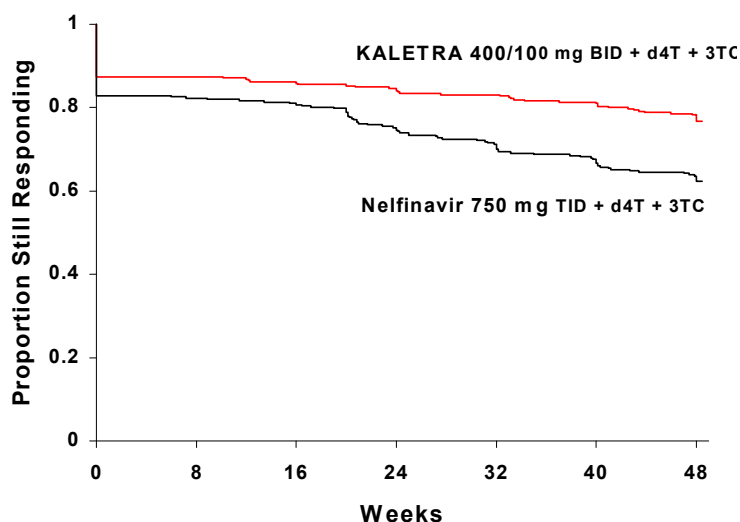
Table 6: Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)						
Baseline Viral Load (HIV-1 RNA copies/mL)	Kaletra +d4T+3TC			Nelfinavir +d4T+3TC		
	<400 copies/mL ¹	<50 copies/mL ²	n	<400 copies/mL ¹	<50 copies/mL ²	n
<30,000	74%	71%	82	79%	72%	87
=30,000 to <100,00	81%	73%	79	67%	54%	79
=100,000 to <250,000	75%	64%	83	60%	47%	72
=250,000	72%	60%	82	44%	33%	89

¹ Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.
² Patients achieved HIV RNA <50 copies/mL at Week 48.

Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was 207 cells/mm³ for the Kaletra arm and 195 cells/mm³ for the nelfinavir arm.

Figure 3 displays the Kaplan-Meier estimates of the time to treatment failure in Study 863. The time of treatment failure was defined as the earliest time a patient experienced virologic failure (two consecutive HIV RNA values demonstrating rebound above 400 copies/mL), a new CDC Class C event, or premature discontinuation from the study.

Figure 3: Time to Treatment Failure (Study 863)



Study M05-730: Kaletra 800/200mg Once Daily + tenofovir DF + emtricitabine compared to Kaletra 400/100mg BD + tenofovir DF + emtricitabine.

Study M05-730 was a randomised, open-label, multicentre trial comparing treatment with Kaletra 800/200 mg once daily plus tenofovir DF and emtricitabine versus Kaletra 400/100 mg twice daily plus tenofovir DF and emtricitabine in 664 antiretroviral treatment-naïve patients. Patients were randomised in a 1:1 ratio to receive either Kaletra 800/200 mg once daily (n = 333) or Kaletra 400/100 mg twice daily (n = 331). Further stratification within each group was 1:1 (tablet versus soft capsule). Patients were administered either the tablet or the soft capsule formulation for 8 weeks, after which all patients were administered the tablet formulation once daily or twice daily for the remainder of the study. Patients were administered emtricitabine 200 mg once daily and tenofovir DF 300 mg once daily. Mean age of patients enrolled was 39 years (range: 19 to 71); 75% were Caucasian, and 78% were male. Mean baseline CD4+ cell count was 216 cells/mm³

(range: 20 to 775 cells/mm³) and mean baseline plasma HIV-1 RNA was 5.0 log₁₀ copies/ml (range: 1.7 to 7.0 log₁₀ copies/mL).

Through 48 weeks of therapy, 78% in the Kaletra once-daily arm and 77% in the Kaletra twice-daily arm achieved and maintained HIV-1 RNA < 50 copies/ml (95% confidence interval for the difference: -5.9% to 6.8%). Mean CD4+ cell count increases at Week 48 were 186 cells/mm³ for the Kaletra once-daily arm and 198 cells/mm³ for the Kaletra twice-daily arm.

Study M97-720: Kaletra capsules BD + stavudine + lamivudine

Study M97-720 is a randomised, blinded, multicentre trial evaluating treatment with Kaletra capsules at three dose levels (Group I: 200/100 mg BD and 400/100 mg BD; Group II: 400/100 mg BD and 400/200 mg BD) plus lamivudine (150 mg BD) and stavudine (40 mg BD) in 100 patients. All patients were converted to open label Kaletra at the 400/100 mg BD dose between weeks 48 and 72 of the study. Patients had a mean age of 35 years (range: 21 to 59), 70% were Caucasian, and 96% were male. Mean baseline CD4 cell count was 338 cells/mm³ (range: 3 to 918 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.9 log₁₀ copies/mL (range: 3.3 to 6.3 log₁₀ copies/mL).

Through 360 weeks of treatment in study 720, the proportion of patients with HIV RNA less than 400 (less than 50) copies/mL was 61% (59%) [n=100], and the corresponding mean increase in CD4 cell count was 501 cells/mm³. Thirty-nine patients (39%) discontinued the study, including 15 (15%) discontinuations due to adverse events and 1 (1%) death. 18 patients demonstrated loss of virologic response (two consecutive rebound HIV-1 RNA values above 400 copies/mL, one rebound HIV-1 RNA value followed by discontinuation, or failure to achieve HIV RNA <400 copies/mL). Genotypic analysis of viral isolates was conducted on these patients and 10 additional patients with isolated HIV-1 RNA values >400 copies/mL after week 24. Results were available from 19 patients and confirmed no primary or active site mutations in protease (amino acids at positions 8, 30, 32, 36, 47, 48, 50, 82, 84 and 90) or protease inhibitor phenotypic resistance.

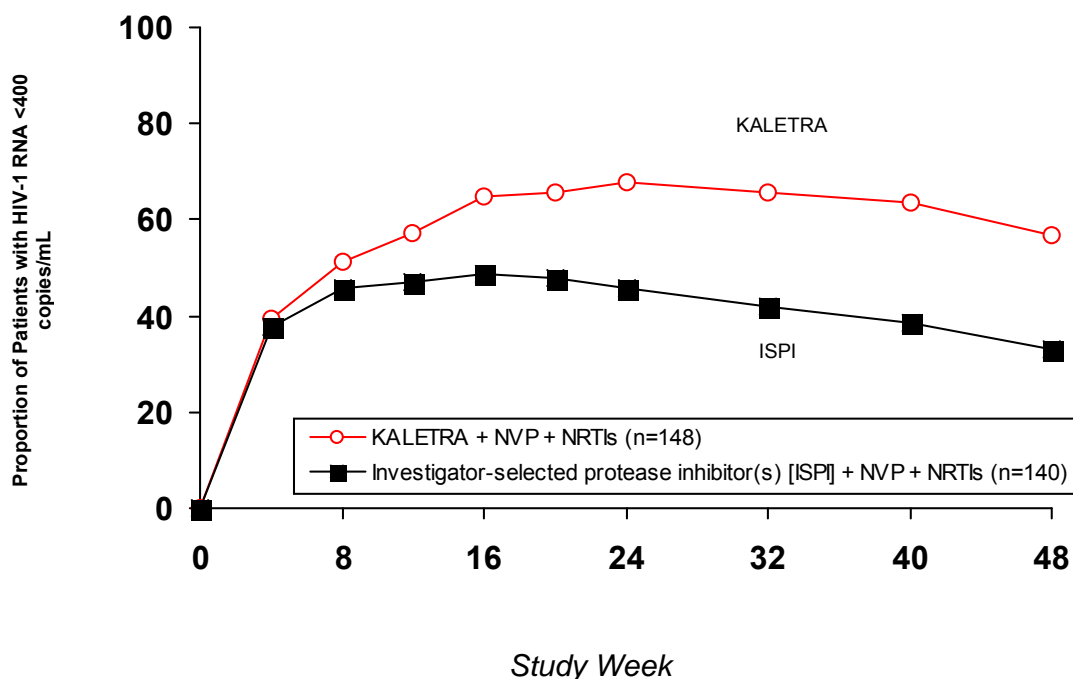
Patients with Prior Antiretroviral Therapy

Study M98-888: Kaletra capsules BD + nevirapine + NRTIs compared to investigator-selected protease inhibitor(s) + nevirapine + NRTIs

Study 888 is a randomised, open-label, multicentre trial comparing treatment with Kaletra capsules (400/100 mg BD) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non- nucleoside reverse transcriptase inhibitor (NNRTI)-naive patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD4 cell count was 322 cells/mm³ (range: 10 to 1059 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.1 log₁₀ copies/mL (range: 2.6 to 6.0 log₁₀ copies/mL).

Treatment response and outcomes of randomised treatment through Week 48 are presented in Figure 4 and Table 7 respectively.

Figure 4: Virologic Response Through Week 48, Study 888*†



* Roche AMPLICOR HIV-1 MONITOR Assay.

† Responders at each visit are patients who had achieved and maintained HIV-1 RNA <400 copies/mL without discontinuation by that visit.

Outcome	Kaletra + nevirapine + NRTIs (n=148)	Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n=140)
Responder* ¹	57%	33%
Virologic Failure ²	24%	41%
Rebound	11%	19%
Never suppressed through Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons ³	14%	13%

* Corresponds to rates at Week 48 in Figure 4.
¹ Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.
² Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
³ Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Study M97-765: Kaletra capsules BD + nevirapine + NRTIs

Study M97-765 was a randomised, blinded, multicentre trial evaluating treatment with Kaletra capsules at two dose levels (400/100 mg BD and 400/200 mg BD) plus nevirapine (200 mg BD)

and two NRTIs in 70 single protease inhibitor experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI) naive patients. Patients had a mean age of 40 years (range 22 to 66), were 73% Caucasian, and were 90% male. Mean baseline CD4 cell count was 372 cells/mm³ (range: 72 to 807 cells/mm³) and mean baseline-plasma HIV-1 RNA was 4.0 log₁₀ copies/mL (range: 2.9 to 5.8 log₁₀ copies/mL).

Through 144 weeks of treatment in study 765, the proportion of patients with HIV RNA less than 400 (less than 50) copies/mL was 54% (50%) [n=70], and the corresponding mean increase in CD4 cell count was 212 cells/mm³. 27 patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

M06-802: Kaletra 800/200mg Once Daily + NRTIs compared to Kaletra 400/100mg BD + NRTIs in Antiretroviral-Experienced, HIV-1 infected patients.

This study was a randomised open-label study comparing the safety, tolerability, and antiviral activity of once daily and twice daily dosing of Kaletra tablets in 599 subjects with detectable viral loads while receiving their current antiviral therapy. Patients were randomised in a 1:1 ratio to receive either Kaletra 800/200 mg once daily (n = 300) or Kaletra 400/100 mg twice daily (n = 299). Patients were administered at least two nucleoside/nucleotide reverse transcriptase inhibitors selected by the investigator. Mean age of patients enrolled was 41 years (range: 21 to 73); 51% were Caucasian, and 66% were male. Mean baseline CD4+ cell count was 254 cells/mm³ (range: 4 to 952 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.3 log₁₀ copies/mL (range: 1.7 to 6.6 log₁₀ copies/mL).

Treatment response and outcomes of randomised treatment through Week 48 are presented in Table 8.

Table 8: Outcomes of Randomised Treatment Through Week 48 (Study 802)		
Outcome	Kaletra Once Daily + NRTIs (n = 300)	Kaletra Twice Daily + NRTIs (n = 299)
Responder ¹	55%	52%
Virologic failure ²	25%	28%
Rebound	12%	14%
Never suppressed through Week 48	13%	14%
Death	1%	1%
Discontinued due to adverse events	4%	6%
Discontinued for other reasons ³	15%	14%
¹ Patients achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48. ² Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48. ³ Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.		

Paediatric Use

Study M98-940

Study M98-940 was an open-label, multicentre trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of Kaletra Oral Solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive (44%) and experienced (56%) paediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomised to either 230 mg lopinavir/57.5 mg ritonavir per m² or 300 mg lopinavir/75 mg ritonavir per m². Naive

patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m² dose. Patients had a mean age of five years (range six months to 12 years) with 14% less than two years. Mean baseline CD4 cell count was 838 cells/mm³ and mean baseline plasma HIV-1 RNA was 4.7 log₁₀ copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA less than 400 copies/mL was 80% for antiretroviral naive patients and 71% for antiretroviral-experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm³ for antiretroviral naive and 284 cells/mm³ for antiretroviral-experienced patients treated through 48 weeks. Premature discontinuations were noted in 2 (2%) subjects prior to week 48. One of these was considered by the investigator to be “unrelated” to study drug, the second “possibly” related to study drug.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m² BD regimen without nevirapine and the 300/75 mg/m² BD regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BD regimen (without nevirapine).

INDICATIONS

Kaletra is indicated for the treatment of HIV-1 infection, in combination with other antiretroviral agents in adults and children aged 2 years and older. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts from controlled clinical studies (see Clinical Trials).

CONTRAINDICATIONS

Kaletra is contraindicated in patients with known hypersensitivity to lopinavir, ritonavir, or any excipients.

Kaletra should not be coadministered concurrently with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 9.

Drug Class	Drug Within Class Not to Be Coadministered
Alpha1-adrenoreceptor antagonist	Alfuzosin hydrochloride
Antibiotics	Fusidic acid
Antihistamines	Astemizole, terfenadine
Antipsychotic	Blonanserin
Benzodiazepines	Midazolam, Triazolam
Ergot derivatives	Ergotamine, Dihydroergotamine, Ergometrine, Methylethergometrine
GI motility agent	Cisapride
Herbal product	St John's Wort (<i>Hypericum perforatum</i>)
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin
Long acting beta-adrenoreceptor agonist	Salmeterol
Neuroleptics	Pimozide
PDE5 inhibitor	Sildenafil * only when used for the treatment of pulmonary arterial hypertension (PAH)
* see Precautions and Drug Interactions for coadministration of sildenafil in patients with erectile dysfunction	

Kaletra Oral Solution is contraindicated in children below the age of 2 years, pregnant women, patients with hepatic and renal failure and patients treated with disulfiram or metronidazole due to the potential risk of toxicity from the excipient propylene glycol.

PRECAUTIONS

Diabetes Mellitus/Hyperglycaemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycaemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

Pancreatitis

Pancreatitis has been observed in patients receiving Kaletra therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to Kaletra has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see PRECAUTIONS: *Lipid Elevations*). Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during Kaletra therapy.

Hepatic Impairment

Kaletra is principally metabolised by the liver. Therefore, caution should be exercised when administering this drug to patients with impaired hepatic function. Kaletra has not been studied in patients with severe hepatic impairment. Pharmacokinetic data suggests increases in lopinavir plasma concentrations of approximately 30% as well as decreases in plasma protein binding in HIV and HCV co-infected patients with mild to moderate hepatic impairment (see PHARMACOLOGY - *Pharmacokinetics*). Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with Kaletra therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of Kaletra treatment.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients after the initiation of Kaletra in conjunction with other antiretroviral agents. In some cases, the hepatic dysfunction was serious; however a definitive causal relationship with Kaletra therapy has not been established.

Resistance/Cross-Resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of Kaletra therapy on the efficacy of subsequently administered protease inhibitors is under investigation (see PHARMACOLOGY).

Haemophilia

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. Neither a causal relationship or a mechanism of action between protease inhibitor therapy and these events has been established.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

QT Interval Prolongation

Post-marketing cases of QT interval prolongation and torsade de pointes have been reported although causality of Kaletra could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalaemia, and with other drugs that prolong the QT interval.

PR Interval Prolongation

Kaletra has been shown to cause modest asymptomatic prolongation of the PR interval in some patients. Rare reports of second or third degree atrioventricular block in patients with underlying structural heart disease and preexisting conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving Kaletra. Kaletra should be used with caution in such patients.

Lipid Elevations

Treatment with Kaletra has resulted in increases in the concentration of total cholesterol and triglycerides (see ADVERSE REACTIONS-Table 11). Triglyceride and cholesterol testing should be performed prior to initiating Kaletra therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See PRECAUTIONS – *Interactions with other medications, HMG-CoA Reductase Inhibitors* for additional information on potential drug interactions with Kaletra and HMG CoA reductase inhibitors.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including Kaletra. During the initial phase of combination antiretroviral treatment when the immune system responds, patients may develop an inflammatory response to asymptomatic or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Effects on Fertility

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels up to 100/50mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.6-fold for lopinavir and 0.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100mg BD).

Use in Pregnancy

Pregnancy Category B3. No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and foetal development toxicities (early resorption, decreased foetal viability, decreased foetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50mg/kg/day were approximately 0.6-fold for lopinavir and 1.6-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100mg BD). In a peri- and post-natal study in rats, a developmental toxicity (a decrease in survival of pups between birth and post-natal day 21) occurred at 40/20mg/kg/day and greater.

No embryonic and foetal developmental toxicity was observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6- fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BD). There are, however, no

adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Kaletra should be used during pregnancy only if the potential benefits justifies the potential risks to the foetus.

Use in Lactation

It is not known whether lopinavir is secreted in human milk. Because of the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed when they are receiving Kaletra. Studies in rats showed that lopinavir is secreted in milk. In a peri- and post-natal study in rats, there was decreased survival of pups between birth and post-natal day 21 when dams were dosed at 40/20mg/kg/day lopinavir/ritonavir and greater. Plasma drug levels were not measured in this study.

Paediatric Use

The safety and pharmacokinetic profiles of Kaletra in paediatric patients below the age of six months have not been established. For paediatric use of Kaletra Oral Solution, see Dosage and Administration. In HIV-infected patients age six months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of Kaletra in paediatric patients in clinical trials is ongoing (see *CLINICAL TRIALS*).

Use in the Elderly

Clinical studies of Kaletra did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of Kaletra in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy

Genotoxicity

Neither lopinavir, ritonavir nor the drug combination was mutagenic or clastogenic in a series of assays for gene mutations (*S. typhimurium*, *E.coli* and mouse lymphoma cells *in-vitro*) and chromosomal damage (human lymphocytes *in-vitro* and mouse micronucleus assay *in-vivo*).

Carcinogenicity

Long-term carcinogenicity studies have been conducted with the lopinavir/ritonavir combination at oral doses of 20/10, 60/30 or 120/60 mg/kg/day in mice, and 10/5, 20/10 and 50/25 mg/kg/day in rats. The incidences of benign hepatocellular adenomas, and hepatocellular adenomas and carcinomas combined were significantly increased in high-dose male and female mice. The incidence of hepatocellular adenomas was increased in high-dose male rats. Lopinavir systemic exposures (AUCs) at the respective high-doses were approximately 2-fold (mice) and 0.5-fold (rats) the human exposure at the recommended therapeutic dose.

Carcinogenicity studies in mice and rats have been carried out with ritonavir alone. In male mice, at dietary levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both hepatocellular adenomas and adenomas and carcinomas combined. Based on AUCs, the exposure of males at the high dose was approximately 4-fold that of the exposure in humans with the recommended therapeutic dose (400/100mg Kaletra BD). In female mice there was a small increase in these tumours at the 200mg/kg dose level. The exposure of females at the high dose was approximately 8-fold that of the exposure in humans. In rats dosed at levels of 7, 15 or 30mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.5-0.7 fold that of the exposure in humans with the 400/100mg Kaletra BD regimen.

The induction of liver tumours in mice by nongenotoxic mechanisms is generally considered to have limited relevance to human risk.

INTERACTIONS WITH OTHER MEDICINES

Kaletra is an inhibitor of CYP3A (cytochrome P450 3A) both *in-vitro* and *in-vivo*. Coadministration of Kaletra and drugs primarily metabolised by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects. Agents that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (greater than 3-fold) when coadministered with Kaletra. Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in Table 9 under CONTRAINDICATIONS.

Kaletra is metabolised by CYP3A. Co-administration of Kaletra and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see PHARMACOLOGY – *Drug – Drug Interactions*). Although not noted with concurrent ketoconazole, coadministration of Kaletra and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Kaletra has been shown to be a potent inducer of CYP2C19 activity. Interactions may exist upon co-administration of Kaletra and drugs primarily metabolised by CYP2C19.

Anti-HIV Agents

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Stavudine and Lamivudine

No change in the pharmacokinetics of lopinavir was observed when Kaletra was given alone or in combination with stavudine and lamivudine.

Didanosine

For Kaletra tablets: It is recommended that didanosine be administered on an empty stomach; therefore, didanosine may be coadministered with Kaletra tablets without food.

For Kaletra Oral Solution: It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after Kaletra Oral Solution.

Zidovudine and Abacavir

Kaletra induces glucuronidation, therefore Kaletra has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Tenofovir

A study has shown Kaletra increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving Kaletra and tenofovir should be monitored for tenofovir-associated adverse events.

All

Increased CPK, myalgia, myositis, and rarely, rhabdomyolysis have been reported with PIs, particularly in combination with NRTIs.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine

No change in the pharmacokinetics of lopinavir was apparent in healthy adult subjects during nevirapine and Kaletra coadministration. Results from a study in HIV-positive paediatric subjects revealed a decrease in lopinavir concentrations during nevirapine coadministration. The effect of nevirapine in HIV-positive adults is expected to be similar to that in paediatric subjects and lopinavir concentrations may be decreased. The clinical significance of the pharmacokinetic

interaction is unknown. Kaletra should not be administered once daily in combination with nevirapine.

Efavirenz

Increasing the dose of Kaletra tablets to 500/125 mg (given as two 200/50 mg tablets and one 100/25 mg tablet) twice daily co-administered with efavirenz 600mg once daily resulted in similar lopinavir concentrations compared to Kaletra tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz (see DOSAGE AND ADMINISTRATION).

Increasing the dose of Kaletra tablets to 600/150 (three (3) tablets) BD coadministered with efavirenz significantly increased the lopinavir plasma concentrations approximately 36% and ritonavir concentrations approximately 56% to 92% compared to Kaletra tablets 400/100 mg BD without efavirenz.

NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with Kaletra.

Kaletra should not be administered once daily in combination with efavirenz.

Delavirdine

Delavirdine has the potential to increase plasma concentrations of lopinavir.

Protease Inhibitors (PIs)

Amprenavir

Kaletra is expected to increase concentrations of amprenavir (amprenavir 750 mg BD plus Kaletra produces increased AUC, similar C_{max} , increased C_{min} , relative to amprenavir 1200 mg BD). Co-administration of Kaletra and amprenavir result in decreased concentrations of lopinavir (see DOSAGE AND ADMINISTRATION). Kaletra should not be administered once daily in combination with amprenavir.

Fosamprenavir

A study has shown that coadministration of Kaletra with fosamprenavir lowers amprenavir and lopinavir concentrations. Appropriate doses of the combination of fosamprenavir and Kaletra with respect to safety and efficacy have not been established. Kaletra should not be administered once daily in combination with fosamprenavir.

Indinavir

Kaletra is expected to increase concentrations of indinavir (indinavir 600 mg BD plus Kaletra produces similar AUC, decreased C_{max} , increased C_{min} relative to indinavir 800 mg TDS. The dose of indinavir may need to be decreased during co-administration of Kaletra 400/100 mg BD (see PHARMACOLOGY – *Drug – Drug Interaction* Table 4).

Nelfinavir

Kaletra is expected to increase concentrations of nelfinavir and increased M8 metabolite of nelfinavir (nelfinavir 1000 mg BD plus Kaletra produces similar AUC, similar C_{max} , increased C_{min} relative to nelfinavir 1250 mg BD). Co-administration of Kaletra and nelfinavir result in decreased concentrations of lopinavir (see DOSAGE AND ADMINISTRATION). Kaletra should not be administered once daily in combination with nelfinavir.

Ritonavir

When Kaletra was coadministered with an additional 100 mg ritonavir twice daily, lopinavir AUC increased 33% and C_{min} increased 64% as compared to Kaletra 400/100 mg (three (3) soft gel capsules) twice daily.

Saquinavir

Kaletra is expected to increase concentrations of saquinavir (saquinavir 800 mg BD plus Kaletra produces increased AUC, increased C_{max} , increased C_{min} relative to saquinavir 1200 mg TDS). The dose of saquinavir may need to be decreased when coadministered with Kaletra 400/100 mg BD (see PHARMACOLOGY – *Drug – Drug Interaction Table 4*).

Tipranavir

In a clinical study of dual-boosted protease inhibitor combination therapy in multiple-treatment experienced HIV-positive adults, tipranavir (500mg twice daily) with ritonavir (200mg twice daily), co-administered with lopinavir/ritonavir (400/100mg twice daily), resulted in a 55% and 70% reduction in lopinavir AUC and C_{min} respectively. The concomitant administration of lopinavir/ritonavir and tipranavir with low dose ritonavir is therefore not recommended.

Other Drugs

Analgesic

Fentanyl

Kaletra inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of fentanyl. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with Kaletra.

Antiarrhythmics (amiodarone, bepridil, systemic lignocaine and quinidine)

Concentrations may be increased when coadministered with Kaletra. Caution is warranted and therapeutic concentration monitoring is recommended when available.

Digoxin

A literature report has shown that coadministration of ritonavir (300 mg every 12 hours) and digoxin resulted in significantly increased digoxin levels. Caution should be exercised when coadministering lopinavir/ritonavir with digoxin, with appropriate monitoring of serum digoxin levels.

Anticancer Agents (e.g. dasatinib, nilotinib, vincristine, vinblastine)

May have their serum concentrations increased when coadministered with lopinavir/ritonavir resulting in the potential for increased adverse events usually associated with these anticancer agents. For nilotinib and dasatinib refer to their prescribing information for dosing instructions.

Anticoagulant:

Warfarin concentrations may be affected when coadministered with Kaletra. It is recommended that INR (international normalized ratio) be monitored.

Antidepressants

Trazodone

Concomitant use of ritonavir and trazodone may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed. If trazodone is used with a CYP3A4 inhibitor such as lopinavir/ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.

Bupropion

Concurrent administration of bupropion with lopinavir/ritonavir will decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion).

Anticonvulsants

Phenobarbital, phenytoin, carbamazepine

These drugs are known to induce CYP3A4 and may decrease lopinavir concentrations. In addition, co-administration of phenytoin and lopinavir/ritonavir resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when

coadministering with lopinavir/ritonavir. Kaletra should not be administered once daily in combination with carbamazepine, phenobarbital or phenytoin.

Antifungals

Ketoconazole and itraconazole may have serum concentrations increased by Kaletra. High doses of ketoconazole and itraconazole (greater than 200 mg/day) are not recommended.

Voriconazole

Co-administration of voriconazole with Kaletra has not been studied. However, a study has shown that administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of Kaletra and voriconazole may result in decreased voriconazole concentrations and the potential for decreased voriconazole effectiveness and should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Otherwise, alternative antifungal therapies should be considered in these patients.

Antigout Agents

Concentrations of colchicine are expected to increase when coadministered with Kaletra. Due to the potential risk of colchicine-associated toxicity such as neuromuscular adverse events and rhabdomyolysis, the concomitant use of colchicine with strong CYP3A4 inhibitors may require close monitoring.

Anti-infective

Moderate increases in clarithromycin AUC are expected when coadministered with Kaletra. For patients with renal or hepatic impairment dose reduction of clarithromycin should be considered.

Anti-mycobacterial

When rifabutin and Kaletra were coadministered for ten days, rifabutin (parent drug and active 25-O-desacetyl metabolite) C_{max} and AUC were increased by 3.5- and 5.7-fold, respectively. On the basis of these data, a rifabutin dose reduction of 75% (i.e. 150 mg every other day or three times per week) is recommended when administered with Kaletra. Further dose reduction of rifabutin may be necessary.

Due to large decreases in lopinavir concentrations, rifampicin should not be used in combination with standard dose Kaletra. The use of rifampicin with Kaletra, may lead to loss of virologic response and possible resistance to Kaletra or to the class of protease inhibitors or other co-administered antiretroviral agents.

In healthy volunteers, co-administration of rifampicin with 800/200mg lopinavir/ritonavir BD resulted in decreases in lopinavir of up to 57%, and co-administration with lopinavir/ritonavir 400/400 mg BD resulted in decreases of up to 7% when compared to lopinavir/ritonavir 400/100 mg BD dosed in the absence of rifampicin. ALT and AST elevations have been noted in studies with doses of lopinavir/ritonavir greater than 400/100 mg BD co-administered with rifampicin and may be dependent on the sequence of dose administration.

The information with regard to the co-administration of Kaletra and rifampicin in the target population of TB-HIV co-infected patients is not available, and in the absence of such data, co-administration of rifampicin and Kaletra should be avoided. In case no alternatives are available, Kaletra should be initiated at standard doses for approximately 10 days prior to addition of rifampicin. Kaletra dose should then be titrated upward. Extreme caution and close monitoring of liver enzymes and plasma drug concentrations is warranted. (See PHARMACOLOGY – *Drug – Drug Interactions*, Table 3 for magnitude of interaction).

Anti-parasitic

Decreases in the therapeutic concentration of atovaquone are possible when coadministered with Kaletra. Increases in atovaquone doses may be necessary.

Corticosteroids

Dexamethasone may induce CYP3A4 and may decrease lopinavir concentrations.

Fluticasone propionate

Concomitant use of Kaletra (lopinavir/ritonavir) and fluticasone propionate can significantly increase fluticasone propionate plasma concentrations and reduce serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported when ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate. Similar findings with concomitant administration of lopinavir/ritonavir and other inhaled corticosteroids that are metabolised similarly to fluticasone, such as budesonide, cannot be excluded. Particular caution should be used when administering lopinavir/ritonavir and any of these inhaled or intranasally administered glucocorticoids. Consider alternatives to fluticasone propionate, particularly for long-term use.

Dihydropyridines Calcium Channel Blockers

Felodipine, nifedipine, nicardipine

May have their serum concentrations increased by Kaletra.

Disulfiram/Metronidazole

Kaletra Oral Solution contains alcohol, which can produce disulfiram like reactions when coadministered with disulfiram or other drugs that produce this reaction, such as metronidazole.

PDE5 inhibitors

Particular caution should be used when prescribing sildenafil, tadalafil or vardenafil for the treatment of erectile dysfunction in patients receiving Kaletra. Coadministration of Kaletra with these drugs is expected to substantially increase their concentrations and may result in increased associated adverse events such as hypotension, and prolonged erection.

Sildenafil:

Use sildenafil for the treatment of erectile dysfunction with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events (see PRECAUTIONS: *Interactions with Other Medicines*).

Concomitant use of sildenafil with Kaletra is contraindicated in pulmonary arterial hypertension (PAH) patients (see CONTRAINDICATIONS and PRECAUTIONS: *Interactions with Other Medicines*).

Tadalafil:

Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events. When tadalafil is administered for the treatment of pulmonary arterial hypertension to patients who are receiving Kaletra, refer to the tadalafil product information for prescribing information.

Vardenafil:

Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.

Herbal Products

Patients on Kaletra should not use products containing St Johns Wort concomitantly, since this combination may be expected to result in reduced plasma concentrations of protease inhibitors. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance to lopinavir or to the therapeutic class of protease inhibitors (see CONTRAINDICATIONS and PRECAUTIONS: *Interactions with Other Medicines*).

HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when coadministered with Kaletra. Since increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis, the combination of these drugs with Kaletra is contraindicated (see CONTRAINDICATIONS).

Atorvastatin is less dependent on CYP3A for metabolism. When atorvastatin was given concurrently with Kaletra, a mean 4.7-fold and 5.9-fold increase in atorvastatin C_{max} and AUC, respectively, was observed. When used with Kaletra, the lowest possible doses of atorvastatin should be administered. In a pharmacokinetic study, coadministration of rosuvastatin and Kaletra in healthy volunteers was associated with an approximately two and five fold increase in rosuvastatin steady state AUC (0 to 24) and C_{max} , respectively. Consideration should be given both to the benefit of lipid lowering by the use of rosuvastatin in patients receiving Kaletra and the potential risks of this increased exposure to rosuvastatin when initiating and up titrating rosuvastatin treatment. Results from a drug interaction study with Kaletra and pravastatin reveal no clinically significant interaction. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A4, and interactions are not expected with Kaletra. If treatment with a HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.

Immunosuppressants

Concentrations of these drugs (e.g. cyclosporin, tacrolimus and sirolimus (rapamycin)) may be increased when coadministered with Kaletra. More frequent therapeutic concentration monitoring is recommended until blood levels of these products have stabilized.

Methadone

Kaletra was demonstrated to lower plasma concentrations of methadone. Monitoring plasma concentrations of methadone is recommended.

Oral Contraceptives or Patch Contraceptives

Since levels of ethinyl oestradiol may be decreased, alternative or additional contraceptive measures are to be used when oestrogen-based oral contraceptives or patch contraceptives and Kaletra are coadministered.

Vasodilating Agents

Co-administration of bosentan and Kaletra increased steady-state bosentan maximum concentrations (C_{max}) and area-under-the-curve (AUC). Refer to the bosentan product information for prescribing information.

Clinically Significant Drug Interactions Are Not Expected

A drug interaction study has revealed no clinically significant interaction between Kaletra administered once or twice daily, and omeprazole or ranitidine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between Kaletra and desipramine (CYP2D6 probe), fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, or fluconazole in patients with normal renal and hepatic function.

ADVERSE EFFECTS

Adults

Treatment-Emergent Adverse Events

Kaletra has been studied in over 2154 HIV-1 infected patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with Kaletra therapy was diarrhoea, which was generally of mild to moderate severity. Rates of discontinuation of randomised therapy due to adverse events, including death, were 5.8% in Kaletra-treated and 4.9% in nelfinavir-treated patients in Study 863.

Treatment-Emergent clinical adverse events of moderate or severe intensity in greater than or equal to 2% of patients treated with combination therapy including Kaletra for up to 48 weeks (Studies 863, 418 and 730) and for up to 360 weeks (Study 720) are presented in Table 10 (antiretroviral -naïve patients) and for up to 48 weeks (Study 888 and 802), 84 weeks (Study 957) and 144 weeks (Study 765) in Table 11 (antiretroviral experienced patients). For other information regarding observed or potentially serious adverse events, please see PRECAUTIONS.

	Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
	LPV/r 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	LPV/r Capsules 800/200 mg QD + TDF + FTC (N=115)	LPV/r Capsules 400/100 mg BID + TDF + FTC (N=75)	LPV/r BID ² + d4T + 3TC (N=100)	LPV/r 800/200 mg QD + TDF +FTC (N=333)	LPV/r 400/100 mg BID + TDF +FTC (N=331)
Gastrointestinal disorders							
Abdominal Distension	0.3%	0.6%	0.9%	0.0%	4.0%	0.3%	0.3%
Abdominal Pain	4.0%	3.1%	2.6%	2.7%	11.0%	0.6%	0.9%
Abnormal faeces	0.0%	0.3%	0.0%	0.0%	8.0%	0.0%	0.0%
Diarrhoea	15.6%	17.1%	15.7%	5.3%	28.0%	16.5%	15.1%
Dyspepsia	2.1%	0.3%	0.0%	1.3%	6.0%	0.0%	0.0%
Flatulence	1.5%	1.2%	1.7%	1.3%	4.0%	0.9%	0.6%
Nausea	6.7%	4.6%	8.7%	8.0%	16.0%	7.2%	5.4%
Vomiting	2.5%	2.4%	3.5%	4.0%	6.0%	3.3%	3.9%
General disorders and administration site conditions							
Asthenia	4.0%	3.4%	0.0%	0.0%	9.0%	0.3%	0.3%
Pain	0.6%	0.0%	0.0%	0.0%	3.0%	0.0%	0.0%
Nervous system disorders							
Headache	2.5%	1.8%	2.6%	2.7%	6.0%	1.5%	0.6%
Parasthesia	0.9%	0.9%	0.0%	0.0%	2.0%	0.0%	0.0%
Psychiatric disorders							
Insomnia	1.5%	1.2%	0.0%	0.0%	3.0%	1.2%	0.0%
Libido decreased	0.3%	0.3%	0.0%	1.3%	2.0%	0.0%	0.3%
Depression	0.6%	1.5%	1.0%	0.0%	0.0%	0.0%	0.0%
Vascular disorders							
Vasodilatation	0.0%	0.0%	0.0%	0.0%	3.0%	0.0%	0.0%
Skin and subcutaneous disorders							
Lipodystrophy acquired	0.6%	0.6%	0.0%	0.0%	12.0%	0.0%	0.0%
Rash	0.6%	1.5%	0.9%	0.0%	5.0%	0.3%	0.6%
Musculoskeletal and connective tissue disorder							
Myalgia	0.6%	0.9%	0.0%	0.0%	2.0%	0.0%	0.0%
Infections and infestations							
Bronchitis	0.0%	0.0%	0.0%	0.0%	2.0%	0.0%	0.3%
Endocrine disorders							
Hypogonadism male	0.0%	0.0%	0.0%	0.0%	2.1%	0.0%	0.0%
Metabolism and nutrition disorders							
Anorexia	0.9%	0.3%	0.9%	1.3%	2.0%	0.3%	0.9%

Table 10: Percentage of Patients with Selected Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in \geq 2% of Adult Antiretroviral-Naïve Patients							
	Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
	LPV/r 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	LPV/r Capsules 800/200 mg QD + TDF + FTC (N=115)	LPV/r Capsules 400/100 mg BID + TDF + FTC (N=75)	LPV/r BID² + d4T + 3TC (N=100)	LPV/r 800/200 mg QD + TDF +FTC (N=333)	LPV/r 400/100 mg BID + TDF +FTC (N=331)
Investigations							
Weight Decreased	0.6%	0.3%	0.0%	0.0%	2.0%	0.0%	0.3%
Reproductive system and breast disorders							
Amenorrhoea	0.0%	0.0%	4.5%	0.0%	0.0%	0.0%	0.0%
¹ Includes adverse events of possible or probable relationship to study drug. ² Includes adverse event data from dose group I (200/100mg BID [N = 16] and 400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to Lopinavir/ritonavir occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II. Definitions: d4T = Stavudine; 3TC = Lamivudine; TDF = Tenofovir; FTC = Emtricitabine							

Table 11: Percentage of Patients with Selected Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in \geq 2% of Adult antiretroviral-Experienced Patients					
	Study 888 (48 Weeks) (%)		Study 957²and Study 765³ (84-144 Weeks) (%)	Study 802 (48 Weeks)	
	Kaletra 400/100 mg BD + NVP + NRTIs (n=148)	Investigator- selected protease inhibitor(s) + NVP + NRTIs (n=140)	Kaletra BD + NNRTI + NRTIs (n= 127)	Kaletra 800/200mg Once daily + NRTIs (n=300)	Kaletra 400/100mg Twice daily +NRTIs (n=299)
Gastrointestinal disorders					
Abdominal pain	2.0%	2.1%	3.9%	2.0%	0.3%
Abdominal pain Upper	N/A	N/A	N/A	0.7%	2.0%
Abnormal faeces	0.0%	0.0%	2.4%	0.0%	0.0%
Diarrhoea	7.4%	9.3%	22.8%	14.0%	11.0%
Dysphagia	2.0%	0.7%	0.0%	0.0%	0.0%
Flatulence	0.7%	2.1%	1.6%	1.0%	1.0%
Nausea	6.8%	16.4%	4.7%	2.7%	7.4%
Vomiting	4.1%	12.1%	1.6%	2.0%	2.7%
General disorders and administration site conditions					
Asthenia	2.7%	6.4%	9.4%	0.3%	0.3%

Table 11: Percentage of Patients with Selected Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult antiretroviral-Experienced Patients					
	Study 888 (48 Weeks) (%)		Study 957 ² and Study 765 ³ (84-144 Weeks) (%)	Study 802 (48 Weeks)	
	Kaletra 400/100 mg BD + NVP + NRTIs (n=148)	Investigator- selected protease inhibitor(s) + NVP + NRTIs (n=140)	Kaletra BD + NNRTI + NRTIs (n= 127)	Kaletra 800/200mg Once daily + NRTIs (n=300)	Kaletra 400/100mg Twice daily +NRTIs (n=299)
Chills	2.0%	0.0%	0.0%	0.0%	0.0%
Pyrexia	2.0%	1.4%	1.6%	0.0%	0.3%
Pain	0.0%	0.0%	3.9%	0.0%	0.0%
Nervous system disorders					
Headache	2.0%	2.9%	2.4%	0.3%	0.0%
Paresthesia	0.0%	1.4%	2.4%	0.0%	0.0%
Vascular disorders					
Hypertension	0.0%	0.0%	2.4%	0.0%	0.0%
Metabolism and nutrition disorders					
Anorexia	0.7%	2.9%	0.0%	0.0%	0.7%
Investigations					
Weight decreased	0.0%	1.4%	3.1%	0.3%	0.3%
Skin and subcutaneous disorders					
Lipodystrophy acquired	0.7%	1.4%	6.3%	0.7%	1.0%
Rash	2.0%	1.4%	2.4%	0.0%	0.0%
Psychiatric disorders					
Insomnia	0.0%	2.1%	2.4%	0.0%	0.3%
Depression	0.7%	2.1%	3.1%	0.3%	0.0%
<p>1 Includes adverse events of possible <u>or</u> probable relationship to study drug.</p> <p>2 Includes adverse event data from patients receiving 400/100 mg BD (n=29) or 533/133 mg BD (n=28) for 84 weeks. Patients received Kaletra in combination with NRTIs and efavirenz.</p> <p>3 Includes adverse event data from patients receiving 400/100 mg BD (n=36) or 400/200 mg BD (n=34) for 144 weeks. Patients received Kaletra in combination with NRTIs and nevirapine.</p> <p>Definitions: NVP = Nevirapine; NRTI = Nucleoside Reverse Transcriptase Inhibitors; NNRTI = Nonnucleoside Reverse Transcriptase Inhibitors</p>					

Treatment-emergent adverse events occurring in less than 2% of adult patients receiving Kaletra in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment with Kaletra and of at least moderate intensity are listed below by system organ class.

Infections and infestations

Bacterial infection, bronchopneumonia, cellulitis, influenza, folliculitis, furunculosis, gastroenteritis, otitis media, perineal abscess, pharyngitis, rhinitis, sialadenitis, sinusitis and viral infection.

Neoplasms benign, malignant and unspecified

Benign neoplasm of skin, lipoma and neoplasm.

Blood and lymphatic system disorders

Anaemia, leukopenia, lymphadenopathy, neutropenia and splenomegaly.

Immune system disorders

Drug hypersensitivity, hypersensitivity, and immune reconstitution syndrome.

Endocrine disorders

Cushing's syndrome and hypothyroidism.

Metabolism and nutrition disorders

Decreased appetite, dehydration, diabetes mellitus, dyslipidaemia, hyperamylasaemia, hyperlipasaemia, hypovitaminosis, increased appetite, lactic acidosis, lipomatosis and obesity.

Psychiatric disorders

Abnormal dreams, affect lability, agitation, anxiety, apathy, confusional state, disorientation, mood swings, nervousness and thinking abnormal.

Nervous System disorders

Ageusia, amnesia, balance disorder, coordination abnormal, cerebral infarction, convulsion, dizziness, dysgeusia, dyskinesia, encephalopathy, extrapyramidal disorder, facial palsy, hypertonia, migraine, neuropathy, neuropathy peripheral, somnolence and tremor.

Eye disorders

Eye disorder and visual disturbance.

Ear and labyrinth disorders

Hyperacusis, tinnitus and vertigo.

Cardiac disorders

Angina pectoris, Atrial fibrillation, atrioventricular block, myocardial infarction, palpitations and tricuspid valve incompetence.

Vascular disorders

Deep vein thrombosis, orthostatic hypotension, thrombophlebitis, varicose vein and vasculitis.

Respiratory, thoracic and mediastinal disorders

Asthma, cough, dyspnea and pulmonary edema.

Gastrointestinal disorders

Abdominal discomfort, , abdominal pain lower, constipation, dry mouth, duodenitis enteritis, enterocolitis, enterocolitis hemorrhagic, eructation, esophagitis, faecal incontinence, gastritis, gastric disorder, gastric ulcer, gastroesophageal reflux disease, hemorrhoids, mouth ulceration, pancreatitis, periodontitis, rectal haemorrhage, stomach discomfort and stomatitis.

Hepatobiliary disorders

Cholangitis, cholecystitis, cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly, jaundice and liver tenderness.

Skin and subcutaneous tissue disorders

Acne, alopecia, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, dry skin, eczema, hyperhidrosis, idiopathic capillaritis, nail disorder, pruritus, rash generalized, rash maculo-papular, seborrhoea, skin discoloration, skin hypertrophy, skin striae, skin ulcer and swelling face.

Musculoskeletal and connective tissue disorder

Arthralgia, arthropathy, back pain, muscular weakness, osteoarthritis, osteonecrosis and pain in extremity.

Renal and urinary disorders

Haematuria, nephritis, nephrolithiasis, renal disorder urine abnormality and urine odour abnormality.

Reproductive system disorders

Breast enlargement, ejaculation disorder, erectile dysfunction, gynecomastia and menorrhagia

General disorders and administration site conditions

Chest pain, cyst, drug interaction, edema, edema peripheral, face edema, fatigue, hypertrophy and malaise.

Investigations

Drug level increased, glucose tolerance decreased and weight increased.

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy including Kaletra with Grade 3 to 4 laboratory abnormalities are presented in Table 12 and 13.

		Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	Limit ¹	KALETRA 400/100 mg BID + d4T +3TC (N = 326)	Nelfinavir 750 mg TID + d4T + 3TC (N = 327)	KALETRA 800/200 mg QD + TDF + FTC (N = 115)	KALETRA 400/100 mg BID + TDF + FTC (N = 75)	KALETRA BID + d4T + 3TC (N = 100)	KALETRA QD + TDF +FTC (N=333)	KALETRA BID + TDF +FTC (N=331)
Chemistry	High							
Glucose	> 250 mg/dL	2%	2%	3%	1%	4%	0%	<1%
Uric Acid	> 12 mg/dL	2%	2%	0%	3%	5%	<1%	1%
SGOT/AST ²	> 180 U/L	2%	4%	5%	3%	10%	1%	2%
SGPT/ALT ²	>215 U/L	4%	4%	4%	3%	11%	1%	1%
GGT	>300 U/L	N/A	N/A	N/A	N/A	10%	N/A	N/A
Total Cholesterol	>300 mg/dL	9%	5%	3%	3%	27%	4%	3%
Triglycerides	>750 mg/dL	9%	1%	5%	4%	29%	3%	6%
Amylase	>2 x ULN	3%	2%	7%	5%	4%	N/A	N/A
Lipase	>2x ULN	NA	NA	NA	NA	NA	3%	5%

		Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)	Study 730 (48 Weeks)	
Variable	Limit ¹	KALETRA 400/100 mg BID + d4T +3TC (N = 326)	Nelfinavir 750 mg TID + d4T + 3TC (N = 327)	KALETRA 800/200 mg QD + TDF + FTC (N = 115)	KALETRA 400/100 mg BID + TDF + FTC (N = 75)	KALETRA BID + d4T + 3TC (N = 100)	KALETRA QD + TDF +FTC (N=333)	KALETRA BID + TDF +FTC (N=331)
Chemistry	Low							
Calculated Creatinine Clearance	<50 mL/min	NA	NA	NA	NA	NA	2%	2%
Hematology	Low							
Neutrophils	0.75 x 10 ⁹ /L	1%	3%	5%	1%	5%	2%	1%

¹ ULN = upper limit of the normal range; N/A = Not Applicable.
² Criterion for Study 730 was >5x ULN.(AST/ALT)

		Study 888 (48 Weeks) (%)		Study 957 ² and Study 765 ³ (84-144 Weeks) (%)	Study 802 (48 weeks) (%)	
Variable	Limit ¹	Kaletra 400/100 mg BD + NVP + NRTIs (n=148)	Investigator -selected protease inhibitor(s) + NVP + NRTIs (n=140)	Kaletra BD + NNRTI + NRTIs (n=127)	Kaletra 800/200mg Once daily + NRTIs (n=300)	Kaletra 400/100mg Twice daily +NRTIs (n=299)
Chemistry	High					
Glucose	>250 mg/dL	1	2	5	2	2
Total Bilirubin	>3.48 mg/dL	1	3	1	1	1
SGOT/AST	>180 U/L	5	11	8	3	2
SGPT/ALT	>215 U/L	6	13	10	2	2
GGT	>300 U/L	N/A	N/A	29	N/A	N/A
Total Cholesterol	>300 mg/dL	20	21	39	6	7
Triglycerides	>750 mg/dL	25	21	36	5	6
Amylase	>2 x ULN	4	8	8	4	4
Lipase	>2x ULN	N/A	N/A	N/A	4	1
Creatine Phosphokinase	>4x ULN	N/A	N/A	N/A	4	5
Chemistry	Low					
Calculated Creatinine	<50mL/min	N/A	N/A	N/A	3	3

Table 13: Grade 3 - 4 Laboratory Abnormalities Reported in ≥ 2% of Adult antiretroviral-Experienced Patients						
		Study 888 (48 Weeks) (%)		Study 957 ² and Study 765 ³ (84-144 Weeks) (%)	Study 802 (48 weeks) (%)	
Variable	Limit ¹	Kaletra 400/100 mg BD + NVP + NRTIs (n=148)	Investigator -selected protease inhibitor(s) + NVP + NRTIs (n=140)	Kaletra BD + NNRTI + NRTIs (n=127)	Kaletra 800/200mg Once daily + NRTIs (n=300)	Kaletra 400/100mg Twice daily +NRTIs (n=299)
Clearance						
Inorganic Phosphorus	<1.5 mg/dL	1	0	2	1	<1
Hematology	Low					
Neutrophils	0.75 x 10 ⁹ /L	1	2	4	3	4
Haemoglobin	<80g/L	1	1	1	1	2
¹ ULN = upper limit of the normal range; N/A = Not Applicable. ² Includes clinical laboratory data from patients receiving 400/100mg BD (n=29) or 533/133mg BD (n=28) for 84 weeks. Patients received Kaletra in combination with NRTIs and efavirenz. ³ Includes laboratory data from patients receiving 400/100 mg BD (n=36) or 400/200 mg BD (n=34) for 144 weeks. Patients received Kaletra in combination with NRTIs and nevirapine. ⁴ Criterion for Study 802 was >5x ULN (AST/ALT)						

Paediatrics

Treatment-Emergent Adverse Events

Kaletra has been studied in 100 paediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Dysgeusia, vomiting, and diarrhoea were the most commonly reported drug related adverse events of any severity in paediatric patients treated with combination therapy including Kaletra for up to 48 weeks in Study 940. A total of 8 children experienced moderate or severe adverse events at least possibly related to Kaletra. Rash (reported in 3%) was the only drug-related clinical adverse event of moderate to severe intensity observed in greater than or equal to 2% of children enrolled.

Laboratory Abnormalities

The percentages of paediatric patients treated with combination therapy including Kaletra with Grade 3 to 4 laboratory abnormalities are presented in Table 14.

Table 14: Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% Paediatric Patients		
Variable	Limit ⁺	Kaletra BD + RTIs (n=100)
Chemistry	High	
Sodium	>149 mEq/L	3.0%
Total bilirubin	> 2.9 x ULN	3.0%
SGOT/AST	> 180 U/L	8.0%

Table 14: Grade 3 to 4 Laboratory Abnormalities Reported in ≥ 2% Paediatric Patients		
Variable	Limit ⁺	Kaletra BD + RTIs (n=100)
SGPT/ALT	> 215 U/L	7.0%
Total Cholesterol	>300 mg/dL or >7.77 mmol/L	3.0%
Amylase	> 2.5 x ULN	7.0% ^{**}
Chemistry	Low	
Sodium	< 130 mEq/L	3.0%
Hematology	Low	
Platelet Count	< 50 x 10 ⁹ /L	4.0%
Neutrophils	< 0.40 x 10 ⁹ /L	2.0%
⁺ ULN = upper limit of the normal range. ^{**} Subjects with Grade 3 to 4 amylase confirmed by elevations in pancreatic amylase.		

Postmarketing Experience

Hepatitis has been reported in patients on Kaletra therapy.

Toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme have been reported.

Bradycardia has been reported.

DOSAGE AND ADMINISTRATION

Tablets

Kaletra tablets should be swallowed whole and not chewed, broken or crushed. Kaletra tablets may be taken with or without food.

Adults

The recommended dosage of Kaletra film coated tablets is 400/100mg (two 200/50mg tablets) twice daily. Kaletra tablets may also be administered as 800/200mg (four 200/50mg tablets) once daily, in patients with less than three lopinavir-associated mutations. There are insufficient data to support the use of once daily administration of Kaletra for adult patients with three or more lopinavir-associated mutations (see PHARMACOLOGY)

Concomitant Therapy: Efavirenz, Nevirapine, Amprenavir, or Nelfinavir

A dose increase of lopinavir/ritonavir to 500/125 mg twice daily (such as two 200/50 mg tablets and one 100/25 mg tablet or 6.25 mL of oral solution) should be considered when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir in treatment experienced patients where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). (see PRECAUTIONS – *Interactions with Other Medicines*).

Paediatric Patients

The adult dose of Kaletra tablets (400/100 mg BD) may be used in children 35 kg or greater. For children weighing less than 35 kg and **able to swallow tablets**, refer to the dosing guideline tables below. Kaletra oral solution is available for children with a body weight of less than 7 kg. Kaletra dosed once daily is not recommended for any paediatric patients.

The following table contains dosing guidelines for Kaletra 100/25 mg tablets in children based on body weight, without efavirenz, nevirapine, nelfinavir or amprenavir.

TABLE 15: Paediatric Dosing Guidelines		
Body Wt (kg)	Recommended number of 100/25 mg Tablets Twice-Daily	Administered Dose
7 < 10	1	100/25mg
≥ 10 < 25	2	200/50mg
≥ 25 < 35	3	300/75mg
≥ 35	4	400/100mg

Concomitant Therapy: Efavirenz, Nevirapine, Nelfinavir or Amprenavir

The following table contains dosing guidelines for Kaletra 100/25 tablets in children based on body weight, when used in combination with efavirenz, nevirapine, nelfinavir, or amprenavir.

TABLE 16: Paediatric Dosing Guidelines with Concomitant Efavirenz, Nevirapine or Amprenavir		
Body Wt (kg)	Recommended number of 100/25 mg Tablets Twice-Daily	Administered Dose
≥ 10 to < 20	2	200/50 mg
≥ 20 to < 30	3	300/75 mg
> 30 kg to 45 kg	4	400/100 mg
> 45 kg	5	500/125 mg

Oral Solution

Adults

Kaletra oral solution is available to patients who cannot take a tablet formulation. The recommended dosage of Kaletra is 5mL of oral solution (400/100mg) twice daily taken with food. Kaletra oral solution may also be administered as 10mL once daily with food, in patients with less than three lopinavir associated mutations.

Paediatric Patients

Total amounts of alcohol and propylene glycol from all medicines, including Kaletra Oral Solution, that are to be given to infants should be taken into account in order to avoid toxicity from these excipients.

The recommended dosage for children 2 years and older is 230/57.5mg/m² (or 12/3 mg/kg for children <15 kg or 10/2.5 mg/kg for children ≥15kg) twice daily taken with food, up to a maximum dose of 400/100mg (5mL) twice daily. In subjects receiving concomitant nevirapine or efavirenz an increase in dosage to 300/75 mg/m² (or 13/3.25 mg/kg for children <15 kg or 11/2.75 mg/kg for children ≥15 kg) twice daily taken with food, should be considered. Kaletra dosed once daily is not recommended for any paediatric patients.

The following tables contain dosing guidelines for Kaletra Oral Solution based on children weighing less than 40kg.

Table 17: Paediatric Dosing Guidelines for Kaletra (80 mg lopinavir/20 mg ritonavir per mL) Oral Solution based on body weight without efavirenz, nevirapine or amprenavir

Weight (kg)	Dose (mg/kg)*	Volume of Oral Solution twice-daily (80 mg lopinavir/20 mg ritonavir per mL)	Administered Dose
7 to < 15 kg	12 mg/kg BD		
7 to 10 kg		1.25 mL	100/25 mg
> 10 to < 15 kg		1.75 mL	140/35 mg
15 to 40 kg	10 mg/kg BD		
15 to 20 kg		2.25 mL	180/45 mg
> 20 to 25 kg		2.75 mL	220/55 mg
> 25 to 30 kg		3.5 mL	280/70 mg
> 30 to 35 kg		4.0 mL	320/80 mg
> 35 to 40 kg		4.75 mL	380/95 mg
> 40 kg	See adult dosage recommendation		

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).

Table 18: Paediatric Dosing Guidelines for Kaletra (80 mg lopinavir/20 mg ritonavir per mL) Oral Solution based on body weight with efavirenz, nevirapine of amprenavir

Weight (kg)	Dose (mg/kg)*	Volume of Oral Solution twice-daily (80 mg lopinavir/20 mg ritonavir per mL)	Administered Dose
7 to < 15 kg	13 mg/kg BD		
7 to 10 kg		1.5 mL	120/30 mg
> 10 to < 15 kg		2.0 mL	160/40 mg
15 to 45 kg	11 mg/kg BD		
15 to 20 kg		2.5 mL	200/50 mg
> 20 to 25 kg		3.25 mL	260/65 mg
> 25 to 30 kg		4.0 mL	320/80 mg
> 30 to 35 kg		4.5 mL	360/90 mg
> 35 to 40 kg		5.0 mL	400/100 mg
> 40 kg	See adult dosage recommendation for concomitant therapy		

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).

OVERDOSAGE



Human experience of acute overdosage with Kaletra is limited. Treatment of overdose with Kaletra should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with Kaletra.

Administration of activated charcoal may reduce absorption of drug if given within one or two hours after ingestion. Since Kaletra is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug. In cases of overdose with Kaletra Oral Solution, consideration may be given to dialysis for removal of propylene glycol.

Kaletra Oral Solution contains 42.4% (v/v) alcohol. Accidental ingestion of the product by a young child could result in significant alcohol related toxicity.

For advice on the management of overdose please contact the Poisons Information Centre in New Zealand on 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

Kaletra is available as 200 mg lopinavir/50 mg ritonavir tablets and 100mg lopinavir/25mg ritonavir tablets. Kaletra 200/50 mg tablets are yellow, ovaloid, film-coated tablets embossed with the Abbott logo  and 'KA'. Kaletra 100/25 mg tablets are pale yellow, debossed with the Abbott logo  and 'KC'.

Kaletra tablets are supplied in High Density Polyethylene (HDPE) bottles closed with propylene caps containing 120 Kaletra 200/50 mg tablets or 60 Kaletra 100/25 mg tablets. Store below 30°C.

Kaletra Oral Solution is a light yellow to golden coloured liquid, supplied in 60mL amber-coloured multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL marked dosing syringe (80 mg lopinavir/20 mg ritonavir per mL). Each pack contains five bottles of 60 mL. Store Kaletra Oral Solution at 2° to 8°C until dispensed. Refrigeration of Kaletra Oral Solution by the patients is not required if used within 42 days and stored below 25°C, however refrigeration by the patient is recommended whenever possible.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

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