KALETRA®
(lopinavir/ritonavir) tablets
(lopinavir/ritonavir) oral solution

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD_4 cell counts in controlled studies of KALETRA of 48 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 144-360 weeks duration.

CLINICAL PHARMACOLOGY

Microbiology

Mechanism of Action

Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

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 (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10-27 nM (0.006-0.017 µg/mL, 1 µg/mL = 1.6 µM) and ranged from 4-11 nM (0.003-0.007 µg/mL) against several HIV-1 clinical isolates (n = 6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65-289 nM (0.04-0.18 µg/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 naïve 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 > 400 copies/mL at Week 24, 32, 40 and/or 48 were analyzed. No evidence of 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 naïve pediatric patients (Study M98-940) 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 (> 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 4 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 - Preclinical Studies

Varying degrees of cross-resistance have been observed among HIV protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during KALETRA therapy.
The antiviral activity in cell culture of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed > 4-fold reduced susceptibility to nelfinavir (n = 13) and saquinavir (n = 4), displayed < 4-fold reduced susceptibility to lopinavir. Isolates with > 4-fold reduced susceptibility to indinavir (n = 16) and ritonavir (n = 3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies - Antiviral Activity of KALETRA in Patients with Previous Protease Inhibitor Therapies

The clinical relevance of reduced susceptibility in cell culture to lopinavir has been examined by assessing the virologic response to KALETRA therapy in treatment-experienced patients, with respect to baseline viral genotype in three studies and baseline viral phenotype in one study.

Virologic response to KALETRA has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. 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 888 and 765 (see INDICATIONS AND USAGE) and study 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 KALETRA [1]

Number of protease inhibitor mutations at baseline[1]	Study 888 (Single protease inhibitor-experienced[2], NNRTI-naïve) n=130	Study 765 (Single protease inhibitor-experienced[3], NNRTI-naïve) n=56	Study 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, L24I, L33F, 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. 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 KALETRA

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	NA	NA

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)

Virologic response to KALETRA therapy with respect to phenotypic susceptibility to lopinavir at baseline was examined in Study 957. In this study 56 NNRTI-naïve patients with HIV RNA > 1000 copies/mL despite previous therapy with at least two protease inhibitors selected from indinavir, nelfinavir, ritonavir and saquinavir were randomized to receive one of two doses of KALETRA in combination with efavirenz and nucleoside reverse transcriptase inhibitors (NRTIs). The EC_{50} values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold the wild-type EC_{50} value. Fifty-five percent (31/56) of these baseline isolates displayed a > 4-fold reduced susceptibility to lopinavir. These 31 isolates had a median reduction in lopinavir susceptibility of 18-fold. Response to therapy by baseline lopinavir susceptibility is shown in Table 3.

Table 3. HIV-RNA Response at Week 48 by Baseline Lopinavir Susceptibility[1]

Lopinavir susceptibility[2] at baseline	HIV RNA < 400 copies/mL (%)	HIV RNA < 50 copies/mL (%)
< 10 fold	25/27 (93%)	22/27 (81%)
> 10 and < 40 fold	11/15 (73%)	9/15 (60%)
≥ 40 fold	2/8 (25%)	2/8 (25%)

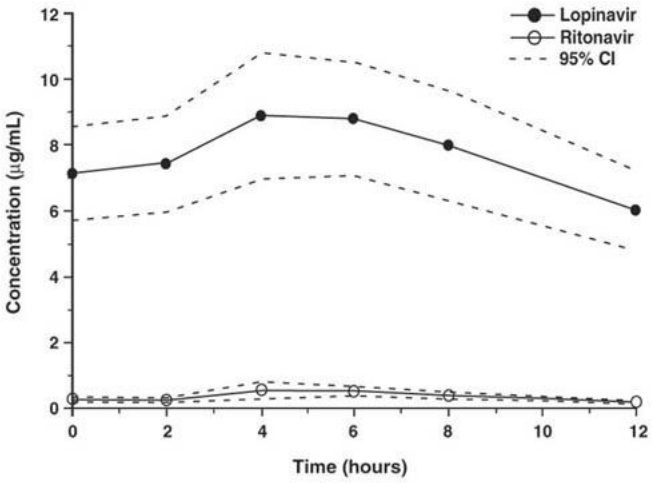
1 Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic.
2 Fold change in susceptibility from wild type.

Pharmacokinetics

The pharmacokinetic properties of lopinavir co-administered 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 metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of KALETRA 400/100 mg twice-daily 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 twice-daily. The in vitro antiviral EC_{50} 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 twice-daily with food for 3 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)



Absorption

In a pharmacokinetic study in HIV-positive subjects (n = 18), multiple dosing with 400/100 mg KALETRA twice-daily for 2 weeks and without meal restriction produced a mean ± 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 and minimum concentration within a dosing interval was 5.6 ± 4.5 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. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA liquid relative to the capsule formulation.

Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg KALETRA tablets are similar to three 133.3/33.3 mg KALETRA capsules under fed conditions with less pharmacokinetic variability.

Effects of Food on Oral Absorption

KALETRA Tablets
No clinically significant changes in C_{max} and AUC were observed following administration of Kaletra tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of KALETRA tablets with a moderate fat meal (500 - 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 26.9% and 17.6%, respectively. Relative to fasting, administration of KALETRA tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9% but not C_{max}. Therefore, Kaletra tablets may be taken with or without food.

KALETRA Oral Solution

Relative to fasting, administration of KALETRA oral solution with a moderate fat meal (500 - 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 80 and 54%, respectively. Relative to fasting, administration of KALETRA oral solution with a high fat meal (872 Kcal, 56% 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 98-99% 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 twice-daily, 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 metabolized 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 $\pm$ 2.3% and 82.6 $\pm$ 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 8 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 $\pm$ 5.75 L/hr (mean $\pm$ SD, n = 19).

Once Daily Dosing

The pharmacokinetics of once daily KALETRA has 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 C_{max} of 14.8 ± 3.5 µg/mL, occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 5.5 ± 5.4 µg/mL and minimum concentration within a dosing interval was 3.2 ± 3.4 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.

PR interval prolongation 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. The maximum mean (95% upper confidence bound) difference from placebo in the PR interval after baseline-correction were 24.9 (21.5, 28.3) and 31.9 (28.5, 35.3) msec for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily KALETRA, respectively (see **WARNINGS AND PRECAUTIONS**).

Special Populations

Pregnancy and Postpartum

In an open-label pharmacokinetic study, 12 HIV-infected pregnant women who were less than 20 weeks of gestation and on combination antiretroviral therapy initially received lopinavir/ritonavir 400 mg/100 mg (two 200/50 mg tablets) twice daily up to a gestational age of 30 weeks. At 30 weeks age of gestation, the dose was increased to 500/125 mg (two 200/50 mg tablets plus one 100/25 mg tablet) twice daily until subjects were 2 weeks postpartum. Plasma concentrations of lopinavir were measured over four 12-hour periods during second trimester (20-24 weeks gestation), third trimester before dose increase (30 weeks gestation), third trimester after dose increase (32 weeks gestation), and at 8 weeks postpartum. The dose increase did not result in a significant increase in the plasma lopinavir concentration (see **PREGNANCY AND LACTATION**).

In another open-label pharmacokinetic study, 19 HIV-infected pregnant women received lopinavir/ritonavir 400/100 mg twice daily as part of combination antiretroviral therapy during pregnancy from before conception. A series of blood samples were collected pre-dose and at intervals over the course of 12 hours in trimester 2 and trimester 3, at birth, and 4–6 weeks postpartum (in women who continued treatment post-delivery) for pharmacokinetic analysis of total and unbound levels of plasma lopinavir concentrations (see **PREGNANCY AND LACTATION**).

The pharmacokinetic data from HIV-1 infected pregnant women receiving lopinavir/ritonavir tablets 400/100 mg twice daily are presented in **Table 4** (see **DOSAGE AND ADMINISTRATION** and **PREGNANCY AND LACTATION**).

Table 4. Mean (%CV) Steady-State Pharmacokinetic Parameters of Lopinavir in HIV-Infected Pregnant Women

Pharmacokinetic Parameter	2nd Trimester n = 17*	3rd Trimester n = 23	Postpartum n = 17**
AUC_{0-12} µg•hr/mL	68.7 (20.6)	61.3 (22.7)	94.3 (30.3)
C_{max}	7.9 (21.1)	7.5 (18.7)	9.8 (24.3)
$C_{predose}$ µg /mL	4.7 (25.2)	4.3 (39.0)	6.5 (40.4)

* n = 18 for C_{max}
** n = 16 for $C_{predose}$

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.

Pediatric Patients

The pharmacokinetics of KALETRA oral solution 300/75 mg/m^2 twice-daily and 230/57.5 mg/m^2 twice-daily have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 twice-daily regimen without nevirapine and the 300/75 mg/m^2 twice-daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice-daily regimen (without nevirapine).

The mean steady-state lopinavir AUC, C_{max}, and C_{min} were 72.6 ± 31.1 µg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 µg/mL, respectively after KALETRA oral solution 230/57.5 mg/m^2 twice-daily without nevirapine (n = 12), and were 85.8 ± 36.9 µg•h/mL, 10.0 ± 3.3 and 3.6 ± 3.5 µg/mL, respectively, after 300/75 mg/m^2 twice-daily with nevirapine (n = 12). The nevirapine regimen was 7 mg/kg twice-daily (6 months to 8 years) or 4 mg/kg twice-daily (> 8 years).

Renal Insufficiency

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 metabolized and eliminated by the liver. Multiple dosing of KALETRA 400/100 mg twice-daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment (n = 12) resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV-infected subjects with normal hepatic function (n = 12). Additionally, the plasma protein

binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31%, respectively). Caution should be exercised when administering KALETRA to subjects with hepatic impairment. KALETRA has not been studied in patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

Drug-drug Interactions

See also **CONTRAINDICATIONS** , **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**.

KALETRA is an inhibitor of the P450 isoform CYP3A in vitro. Co-administration of KALETRA and drugs primarily metabolized 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 metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized 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, co-administration 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 co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in Table 5 (effect of other drugs on lopinavir) and Table 6 (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 Table 13 in **DRUG INTERACTIONS**.

Table 5. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug (See DRUG INTERACTIONS - Table 13 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	**Dose of Co-administered Drug (mg)**	**Dose of KALETRA (mg)**		**Ratio (in combination with Co-administered drug-/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00**		
			n	**C_{max}**	**AUC**	**C_{min}**
Amprenavir	750 BID, 10 d	400/100 capsule BID, 21 d	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Boceprevir	800 mg q8h, 6 d	400/100 tablet BID, 22 d	13	0.70 (0.65, 0.77)	0.66 (0.60, 0.72)	0.57 (0.49, 0.65)
Efavirenz[1]	600 QHS, 9 d	400/100 capsule BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 QHS, 9 d	500/125 tablet BID, 10 d	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 QHS, 9 d	600/150 tablet BID, 10 d with efavirenz 600 mg QHS compared to 400/100 BID alone	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Fosamprenavir[2]	700 BID plus ritonavir 100 BID, 14 d	400/100 capsule BID, 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole	200 single dose	400/100 capsule BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 BID, 10 d	400/100 capsule BID, 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 BID, steady-state (> 1 yr)[3]	400/100 capsule BID, steady-state (> 1 yr)	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 QD, 2 wk; BID 1 wk[4]	300/75 mg/m^2 oral solution BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)

Omeprazole	40 QD, 5 d	400/100 tablet BID, 10 d	12	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)
		800/200 tablet QD, 10 d	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
Pravastatin	20 QD, 4 d	400/100 capsule BID, 14 d	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 BID, 10 d	12	0.99 (0.95, 1.03)	0.97 (0.93, 1.01)	0.90 (0.85, 0.95)
		800/200 tablet QD, 10 d	11	0.98 (0.95, 1.01)	0.96 (0.90, 1.02)	0.85 (0.67, 1.08)
Rifabutin	150 QD, 10 d	400/100 capsule BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Rifampin	600 QD, 10 d	400/100 capsule BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 QD, 14 d	800/200 capsule BID, 9 d[5]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 QD, 14 d	400/400 capsule BID, 9 d[6]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
					Co-administration of standard dose of KALETRA and rifampin is not recommended (see **DRUG INTERACTIONS**).	
Ritonavir[3]	100 BID, 3-4 wk	400/100 capsule BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Telaprevir	750 mg q8h, 10 d	400/100 BID, 20 d	12[x]	0.96 (0.87, 1.05)	1.06 (0.96, 1.17)	1.14 (0.96, 1.36)
Tenofovir[7]	300 mg QD, 14 d	400/100 capsule BID, 14 d	24	NC†	NC†	NC†

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

1 The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

2 Data extracted from the fosamprenavir package insert.

3 Study conducted in HIV-positive adult subjects.

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

5 Titrated to 800/200 BID as 533/133 BID x 1 d, 667/167 BID x 1 d, then 800/200 BID x 7 d, compared to 400/100 BID x 10 days alone.

6 Titrated to 400/400 BID as 400/200 BID x 1 d, 400/300 BID x 1 d, then 400/400 BID x 7 d, compared to 400/100 BID x 10 days alone.

7 Data extracted from the tenofovir package insert.

* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.

† NC = No change.

X N=12 for test arm, 19 for reference arm

Table 6. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA (See DRUG INTERACTIONS - Table 13 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	**Dose of Co-administered Drug (mg)**	**Dose of KALETRA (mg)**		**Ratio (in combination with KALETRA/alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00**		
			n	**C_{max}**	**AUC**	**C_{min}**
Amprenavir[1]	750 BID, 10 d combo vs. 1200 BID, 14 d alone	400/100 capsule BID, 21 d	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Atorvastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Boceprevir	800 mg q8h, 6 d	400/100 tablet BID, 22 d	13[x]	0.50 (0.45, 0.55)	0.55 (0.49, 0.61)	0.43 (0.36, 0.53)

Desipramine[2]	100 single dose	400/100 capsule BID, 10 d	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	N/A
Efavirenz	600 QHS, 9 d	400/100 capsule BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum®)	400/100 capsule BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Fosamprenavir [3]	700 BID plus ritonavir 100 BID, 14 d	400/100 capsule BID, 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir[1]	600 BID, 10 d combo nonfasting vs. 800 TID, 5 d alone fasting	400/100 capsule BID, 15 d	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 BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Lamotrigine	100 BID, 12 d vs. 100 BID, 8 d alone	400/100 capsule BID, 12 d	18	0.54 (0.49, 0.58)	0.5 (0.47, 0.54)	0.44 (0.40, 0.47)
	200 BID, 9 d vs. 100 BID, 8 d alone	400/100 capsule BID, 9 d	15	1.03 (0.90, 1.17)	0.91 (0.82, 1.02)	0.79 (0.69, 0.90)
Maraviroc	300 mg BID	400/100 capsule BID	11	1.97 (1.66, 2.34)	3.95 (3.43, 4.56)	9.24 (7.98, 10.7)
Methadone	5 single dose	400/100 capsule BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nelfinavir[1]	1000 BID, 10 d combo vs. 1250 BID, 14 d alone	400/100 capsule BID, 21 d	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 QD, 14 d; BID, 6 d	400/100 capsule BID, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho Novum®)	400/100 capsule BID, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pravastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	150 QD, 10 d; combo vs. 300 QD, 10 d; alone	400/100 capsule BID, 10 d	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)
Rifabutin + 25-*O*-desacetyl rifabutin[4]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Saquinavir[1]	800 BID, 10 d combo vs. 1200 TID, 5 d alone,	400/100 capsule BID, 15 d	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
	1200 BID, 5 d combo vs. 1200 TID 5 d alone	400/100 capsule BID, 20 d	10	6.44 (5.59, 7.41)	9.91 (8.28, 11.86)	16.54 (10.91, 25.08)
Telaprevir	750 mg q8h, 10 d	400/100 BID, 20 d	12[Y]	0.47 (0.41, 0.52)	0.46 (0.41, 0.52)	0.48 (0.40, 0.56)
Tenofovir[5]	300 mg QD, 14 d	400/100 capsule BID, 14 d	24	NC[†]	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

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 Data extracted from the fosamprenavir package insert.

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

5 Data extracted from the tenofovir package insert.

* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.

N/A = Not available.

† NC = No change.

X N=12 for Cmin (test arm)

Y N=12 for the test arm, 14 for reference arm

PRE-CLINICAL SAFETY DATA

Acute, Subacute and Chronic Toxicity

Repeat-dose toxicity studies in rodents and dogs identified major target organs as the liver, kidney, thyroid, spleen and circulating red blood cells. Hepatic changes indicated cellular swelling with focal degeneration. While exposure eliciting these changes were comparable to human clinical exposure, dosages in animals were over 6-fold the recommended clinical dose. Mild renal tubular degeneration was confined to mice exposed with at least twice the recommended human exposure; the kidney was unaffected in rats and dogs. Reduced serum thyroxine led to an increased release of TSH with resultant follicular cell hypertrophy in the thyroid glands of rats. These changes were reversible with withdrawal of the active substance and were absent in mice and dogs. Coombs-negative anisocytosis and poikilocytosis were observed in rats, but not in mice or dogs. Enlarged spleens with histiocytosis were seen in rats but not other species. Serum cholesterol was elevated in rodents but not dogs, while triglycerides were elevated only in mice.

Carcinogenesis and Mutagenesis

Long-term carcinogenicity studies of lopinavir/ritonavir in mice revealed a non-genotoxic, mitogenic induction of liver tumors, generally considered to have little relevance to human risk. Carcinogenicity studies in rats revealed no tumorigenic findings. Lopinavir was not found to be mutagenic or clastogenic in a battery of *in vitro* assays including the Ames bacterial reverse mutation assay, the mouse lymphoma assay, and chromosomal aberration assays in human lymphocytes. Lopinavir/ritonavir was not found to be mutagenic or clastogenic in *in vivo* assays using the mouse micronucleus assay.

DESCRIPTION OF CLINICAL STUDIES

Patients Without Prior Antiretroviral Therapy

Study 863: KALETRA capsules twice-daily + stavudine + lamivudine compared to nelfinavir three-times-daily + stavudine + lamivudine

Study 863 was a randomized, double-blind, multicenter trial comparing treatment with KALETRA capsules (400/100 mg twice-daily) plus stavudine and lamivudine versus nelfinavir (750 mg three-times-daily) plus stavudine and lamivudine in 653 antiretroviral treatment naïve patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD_4 cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 2.6 to 6.8 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 7.

Table 7. Outcomes of Randomized Treatment Through Week 48 (Study 863)

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

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 < 400 copies/mL (75% vs. 62%, respectively) and HIV RNA < 50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV RNA level subgroups is presented in Table 8.

Table 8. 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 < 100,000	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 CD_4 cell count was 207cells/mm^3 for the KALETRA arm and 195 cells/mm^3 for the nelfinavir arm.

Study 730: KALETRA Tablets once daily + tenofovir DF + emtricitabine compared to KALETRA Tablets twice daily + tenofovir DF + emtricitabine.

Study 730 was a randomized, open-label, multicenter 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 randomized 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 vs. capsule). Patients administered the capsule were switched to the tablet formulation at Week 8 and maintained on their randomized dosing schedule. 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/mm^3 (range: 20 to 775 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL (range: 1.7 to 7.0 log10 copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 9.

Table 9. Outcomes of Randomized Treatment Through Week 48 (Study 730)

Outcome	KALETRA once daily +TDF+FTC (N = 333)	KALETRA twice daily +TDF+FTC (N = 331)
Responder[1]	78%	77%
Virologic failure[2] Rebound Never suppressed through Week 48	10% 5% 5%	8% 5% 3%
Death	1%	<1%
Discontinued due to adverse event	4%	3%
Discontinued for other reasons[3]	8%	11%

1 Patients achieved and maintained confirmed HIV 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.

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/mm^3 for the KALETRA once daily arm and 198 cells/mm^3 for the KALETRA twice daily arm.

Patients with Prior Antiretroviral Therapy

Study 888: KALETRA capsules twice-daily + nevirapine + NRTIs compared to investigator-selected protease inhibitor(s) + nevirapine + NRTIs

Study 888 was a randomized, open-label, multicenter trial comparing treatment with KALETRA capsules (400/100 mg twice-daily) 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)-naïve patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD_4 cell count was 322 cells/mm^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 $\log_{10}$ copies/mL (range: 2.6 to 6.0 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 10.

Table 10. Outcomes of Randomized Treatment Through Week 48 (Study 888)

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 Never suppressed through Week 48	11% 13%	19% 23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons[3]	14%	13%

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.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the investigator-selected protease inhibitor(s) arm with HIV RNA < 400 copies/mL (57% vs. 33%, respectively).

Through 48 weeks of therapy, the mean increase from baseline in CD_4 cell count was 111 cells/mm^3 for the KALETRA arm and 112 cells/mm^3 for the investigator-selected protease inhibitor(s) arm.

Study 802: KALETRA Tablets 800/200 mg Once Daily Versus 400/100 mg Twice Daily when Coadministered with Nucleoside/Nucleotide Reverse Transcriptase Inhibitors in Antiretroviral-Experienced, HIV-1 Infected Subjects

M06-802 was a randomized 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 randomized 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. The enrolled population was moderately PI-experienced with more than half of patients having never received prior PI and around 80% of patients presenting a viral strain with less than 3 PI mutations. 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/mm^3 (range: 4 to 952 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.3 log_{10} copies/mL (range: 1.7 to 6.6 log_{10} copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 11.

Table 11. Outcomes of Randomized 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] Rebound Never suppressed through Week 48	25% 12% 13%	28% 14% 14%
Death	1%	1%
Discontinued due to adverse event	4%	6%
Discontinued for other reasons[3]	15%	14%

1 Patients achieved and maintained confirmed HIV 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.

Other Studies

Study 720: KALETRA twice-daily + stavudine + lamivudine
Study 765: KALETRA twice-daily + nevirapine + NRTIs

Study 720 (patients without prior antiretroviral therapy) and study 765 (patients with prior protease inhibitor therapy) were randomized, blinded, multi-center trials evaluating treatment with KALETRA at up to three dose levels (200/100 mg twice-daily [720 only], 400/100 mg twice-daily, and 400/200 mg twice-daily). In Study 720, all patients switched to 400/100 mg twice-daily between Weeks 48-72. Patients in study 720 had a mean age of 35 years, 70% were Caucasian, and 96% were male, while patients in study 765 had a mean age of 40 years, 73% were Caucasian, and 90% were male. Mean (range) baseline CD_4 cell counts for patients in study 720 and study 765 were 338 (3-918) and 372 (72-807) cells/mm^3, respectively. Mean (range) baseline plasma HIV-1 RNA levels for patients in study 720 and study 765 were 4.9 (3.3 to 6.3) and 4.0 (2.9 to 5.8) log_{10} copies/mL, respectively.

Through 360 weeks of treatment in study 720, the proportion of patients with HIV RNA < 400 (< 50) copies/mL was 61% (59%) [n = 100], and the corresponding mean increase in CD_4 cell count was 501 cells/mm^3. Thirty-nine patients (39%) discontinued the study, including 15 (15%) discontinuations due to adverse events and 1 (1%) death. Through 144 weeks of treatment in study 765, the proportion of patients with HIV RNA < 400 (< 50) copies/mL was 54% (50%) [n = 70], and the corresponding mean increase in CD_4 cell count was 212 cells/mm^3. Twenty-seven patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

Pediatric Studies

Study M98-940: An Open-Label Phase I/II Study of Lopinavir/Ritonavir in Combination with Reverse Transcriptase Inhibitors in HIV-Infected Children

Study M98-940 was an open-label, multicenter 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 naïve (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naïve 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 m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD_4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 log_{10} copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA < 400 copies/mL was 80% for antiretroviral naïve patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD_4 cell count was 404 cells/mm^3 for antiretroviral naïve and 284 cells/mm^3 for antiretroviral experienced patients treated through 48 weeks. At 48 weeks, two patients (2%) had prematurely discontinued the study. One antiretroviral naïve patient prematurely discontinued secondary to an adverse event attributed to KALETRA, while one antiretroviral experienced patient prematurely discontinued secondary to an HIV-related event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 oral solution twice-daily regimen without nevirapine and the 300/75 mg/m^2 oral solution twice-daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice-daily regimen (without nevirapine).

KONCERT/PENTA 18: Kaletra Once Daily Randomized Trial of the Pharmacokinetics, Safety and Efficacy of Twice Daily versus Once Daily Lopinavir/Ritonavir Tablets Dosed by Weight as Part of Combination Antiretroviral Therapy in HIV-1 Infected Children/Paediatric European Network for the Treatment of AIDS

KONCERT/PENTA18 is a prospective multicenter, randomized, open-label study that evaluated the pharmacokinetic profile, efficacy, and safety of twice-daily versus once-daily dosing of lopinavir/ritonavir 100/25 mg tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged < 18 years, ≥ 15 kg in weight, receiving cART that included lopinavir/ritonavir, HIV-1 ribonucleic acid (RNA) < 50 copies/mL for at least 24 weeks and able to swallow tablets. At week 48, the efficacy and safety with twice daily dosing (n=87) in the pediatric population given lopinavir/ritonavir 100/25 mg tablets was consistent with the efficacy and safety findings in previous adult and pediatric studies using lopinavir/ritonavir twice daily. Once daily dosing of lopinavir/ritonavir tablets was not bioequivalent to twice daily dosing for lopinavir/ritonavir.

CONTRAINDICATIONS

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

Co-administration of KALETRA is contraindicated 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 12.

Table 12. Drugs That Are Contraindicated With KALETRA

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA
Alpha1-adrenoreceptor antagonist	alfuzosin HCl
Antianginal	ranolazine
Antiarrhythmic	dronedarone
Antibiotics	fusidic acid
Anticancer Agents	neratinib, apalutamide
Antigout	colchicine in patients with renal and/or hepatic impairment
Antihistamines	astemizole, terfenadine
Antipsychotic	blonanserin, lurasidone, pimozide
Benzodiazepines	midazolam, triazolam
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	cisapride
Herbal product	St. John's Wort (Hypericum perforatum)
Hepatitis C direct acting antiviral	elbasvir/grazoprevir
Lipid-modifying agents HMG-CoA reductase inhibitors Microsomal triglyceride transfer protein (MTTP) Inhibitor	 lovastatin, simvastatin lomitapide
Long acting beta-adrenoceptor agonist	salmeterol
PDE5 enzyme inhibitor	sildenafil* (Revatio®) only when used for the treatment of pulmonary arterial hypertension (PAH)

* see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS for co-administration of sildenafil in patients with erectile dysfunction.

WARNINGS AND PRECAUTIONS

ALERT: Find out about medicines that should NOT be taken with KALETRA.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics** – Drug-drug Interactions**, CONTRAINDICATIONS and DRUG INTERACTIONS**).

Antigout agents
Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Anti-mycobacterial

Standard dose Kaletra should not be coadministered with rifampin because large decreases in lopinavir concentrations may significantly decrease the therapeutic effect (see **DRUG INTERACTIONS)**.

Co-administration of bedaquiline with strong CYP3A4 inhibitors may increase the systemic exposure of bedaquiline, which could potentially increase the risk of bedaquiline-related adverse reactions (see **DRUG INTERACTIONS**). Bedaquiline must be used cautiously with lopinavir/ritonavir, only if the benefit of co-administration outweighs the risk.

Co-administration of delamanid with a strong inhibitor of CYP3A (lopinavir/ritonavir) may slightly increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **DRUG INTERACTIONS**).

Antipsychotics

Caution should be exercised when lopinavir/ritonavir is co-administered with quetiapine. Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase, which may lead to quetiapine-related serious and life-threatening adverse reactions (see **DRUG INTERACTIONS**).

Corticosteroids

Concomitant use of lopinavir/ritonavir and inhaled, injectable, or intranasal fluticasone, budesonide, triamcinolone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.

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 lopinavir/ritonavir has been co-administered with inhaled or intranasally administered fluticasone propionate or budesonide, or injectable triamcinolone (see **DRUG INTERACTIONS**).

Type 5 Phosphodiesterase (PDE5) Inhibitors

Co-administration of lopinavir/ritonavir with avanafil is not recommended. Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil for the treatment of erectile dysfunction in patients receiving KALETRA. Co-administration of KALETRA with these drugs is expected to substantially increase their concentrations and may result in an increase in associated adverse events including hypotension, syncope, visual changes and prolonged erection. Concomitant use of sildenafil with lopinavir/ritonavir is contraindicated in pulmonary arterial hypertension (PAH) patients (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS** and the complete prescribing information for sildenafil, tadalafil, vardenafil and avanafil.)

Herbal Products

Patients on lopinavir/ritonavir should not use products containing St. John's Wort *(Hypericum perforatum)* because coadministration may be expected to reduce plasma concentrations of protease inhibitors. This may result in loss of therapeutic effect and development of resistance to lopinavir or to the therapeutic class of protease inhibitors (see **CONTRAINDICATIONS and DRUG INTERACTIONS**).

HMG-CoA Reductase Inhibitors

Concomitant use of KALETRA with lovastatin or simvastatin is contraindicated (see **CONTRAINDICATIONS**). Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with rosuvastatin or with other HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs (see DRUG INTERACTIONS).

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), coadministered 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.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia 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 hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia 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.

Consideration should be given to the monitoring of blood glucose.

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 **WARNINGS AND 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.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.

Hepatic Impairment

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment. 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 **CLINICAL 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 or hepatic decompensation. There have been post-marketing 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.

Elevated transaminases with or without elevated bilirubin levels have been reported in HIV-1 mono-infected and uninfected patients as early as 7 days 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. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of KALETRA treatment.

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 **CLINICAL PHARMACOLOGY: Microbiology**).

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia 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. A causal relationship between protease inhibitor therapy and these events has not been established.

PR Interval Prolongation

Lopinavir/ritonavir 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 lopinavir/ritonavir. Lopinavir/ritonavir should be used with caution in such patients (see **CLINICAL PHARMACOLOGY**).

Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS** – Tables 14 - 16). 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 **WARNINGS AND PRECAUTIONS: *HMG-CoA Reductase Inhibitors*** for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

Weight and Metabolic Parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

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, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis) which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

Geriatric Use

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.

Pediatric Use

The safety and pharmacokinetic profiles of KALETRA in pediatric patients below the age of six months have not been established. For pediatric use of KALETRA oral solution, see **DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS,** and **OVERDOSAGE**. In HIV-infected patients age six months to 18 years, the adverse event profile seen during clinical trials was similar to that for adult patients. KALETRA should not be administered once daily in pediatric patients.

Serious Toxicity in Neonates

KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities (see **WARNINGS AND PRECAUTIONS, Pediatric Use**, and **OVERDOSAGE**). A safe and effective dose of KALETRA oral

solution in this patient population has not been established.

KALETRA oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Post-marketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving KALETRA oral solution.

All infants administered Kaletra should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to KALETRA oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Total amounts of alcohol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients.

DRUG INTERACTIONS

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both in vitro and in vivo. Co-administration of KALETRA and drugs primarily metabolized 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 (see **WARNINGS AND PRECAUTIONS**). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (> 3-fold) when co-administered with KALETRA. Drugs that are contraindicated specifically due to the expected magnitude of interaction and potential for serious adverse events are listed in **Table 12** under **CONTRAINDICATIONS**.

KALETRA is metabolized by CYP3A. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see **WARNINGS AND PRECAUTIONS**). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

These examples are a guide and not considered a comprehensive list of all possible drugs that may interact with lopinavir/ritonavir. The healthcare provider should consult appropriate references for comprehensive information.

Table 13 provides a listing of established or potentially clinically significant drug interactions. Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction. (See **CLINICAL PHARMACOLOGY** for Magnitude of Interaction – Table 5 and Table 6).

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of lopinavir or Concomitant Drug**	**Clinical Comment**
HIV-Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: Efavirenz*, Nevirapine*	↓ Lopinavir	KALETRA dose increase is recommended in all patients (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY). 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 resulted in similar lopinavir concentrations compared to KALETRA tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz. Increasing the dose of KALETRA tablets to 600/150 mg (given as three 200/50 mg tablets) twice-daily co-administered with efavirenz resulted in significantly higher lopinavir plasma concentrations compared to KALETRA tablets 400/100 mg twice-daily without efavirenz.
Non-nucleoside Reverse Transcriptase Inhibitor: Delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	↓ Etravirine	Concomitant use of KALETRA with etravirine causes a decrease in the plasma concentrations of etravirine, but no dose adjustment is required. Refer to the etravirine prescribing information.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	↑ Rilpivirine	Concomitant use of KALETRA with rilpivirine causes an increase in the plasma concentrations of rilpivirine, but no dose adjustment is required. Refer to the rilpivirine prescribing information.
Nucleoside Reverse Transcriptase Inhibitor: Didanosine		KALETRA tablets can be administered simultaneously with didanosine 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 (given with food).
Nucleoside Reverse Transcriptase Inhibitor: Tenofovir	↑ Tenofovir	KALETRA increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving KALETRA and tenofovir should be monitored for tenofovir-associated adverse events.

Nucleoside Reverse Transcriptase Inhibitor: Abacavir Zidovudine	↓ Abacavir ↓ Zidovudine	KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.
HIV-Protease Inhibitor: Amprenavir*	↑ Amprenavir (amprenavir 750 mg BID + KALETRA produces ↑ AUC, similar C_{max}, ↑ C_{min}, relative to amprenavir 1200 mg BID) ↓ Lopinavir	KALETRA should not be administered once daily in combination with amprenavir.
HIV-Protease Inhibitor: Fosamprenavir/Ritonavir	↓ Amprenavir ↓ Lopinavir	An increased rate of adverse events has been observed with co-administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-Protease Inhibitor: Indinavir*	↑ Indinavir (indinavir 600 mg BID + KALETRA produces similar AUC, ↓ C_{max}, ↑ C_{min} relative to indinavir 800 mg TID)	Decrease indinavir dose to 600 mg BID, when co-administered with KALETRA 400/100 mg BID (see **CLINICAL PHARMACOLOGY** - Table 6). KALETRA once daily has not been studied in combination with indinavir.
HIV-Protease Inhibitor: Nelfinavir*	↑ Nelfinavir (nelfinavir 1000 mg BID + KALETRA produces similar AUC, similar C_{max}, ↑ C_{min} relative to nelfinavir 1250 mg BID) ↑ M8 metabolite of nelfinavir ↓ Lopinavir	KALETRA should not be administered once daily with in combination with nelfinavir.
HIV-Protease Inhibitor: Saquinavir*	↑ Saquinavir	The saquinavir dose is 1000 mg BID, when co-administered with KALETRA 400/100 mg BID. KALETRA once daily has not been studied in combination with saquinavir.
HIV-Protease Inhibitor: Ritonavir*	↑ Lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
HIV-Protease Inhibitor: Tipranavir*	↓ Lopinavir AUC and C_{min}	KALETRA should not be administered with tipranavir (500 mg twice-daily) co-administered with ritonavir (200mg twice-daily)
Hepatitis C Direct Acting Antivirals: Boceprevir*	↓ Boceprevir ↓ Lopinavir ↓ Ritonavir	Concomitant administration of boceprevir and KALETRA resulted in reduced boceprevir, lopinavir and ritonavir steady-state exposure. It is not recommended to co-administer KALETRA and boceprevir.
Glecaprevir/pibrentasvir		Concomitant administration of glecaprevir/pibrentasvir and lopinavir/ritonavir is not recommended due to an increased risk of ALT elevations associated with increased GLE exposure.
Hepatitis C Direct Acting Antivirals: Ombitasvir/paritaprevir/ritonavir and dasabuvir	↑ Ombitasvir ↑ Paritaprevir ↑ Ritonavir	Concentrations of ombitasvir, paritaprevir, and ritonavir may be increased when co-administered with lopinavir/ritonavir, therefore, co-administration is not recommended.
Hepatitis C Direct Acting Antivirals: Simeprevir	↑ Simeprevir	Concomitant use of KALETRA and simeprevir may result in increased plasma concentrations of simeprevir. It is not recommended to co-administer KALETRA and simeprevir.
Sofosbuvir/velpatasvir/voxilaprevir		Concomitant administration of sofosbuvir/velpatasvir/voxilaprevir and lopinavir/ritonavir is not recommended due to the potential for increased toxicity, which may negatively impact compliance.
Hepatitis C Direct Acting Antivirals: Telaprevir*	↓ Telaprevir ↔ Lopinavir	Concomitant administration of telaprevir and KALETRA resulted in reduced telaprevir steady-state exposure, while the lopinavir steady-state exposure was not affected.
HIV CCR5-antagonist: Maraviroc*	↑ Maraviroc	Concurrent administration of maraviroc with KALETRA will increase plasma levels of maraviroc. The dose of maraviroc should be decreased during co-administration with lopinavir/ritonavir 400/100 mg BID. For further details, see complete prescribing information for maraviroc.
Other Agents		
Analgesics: Fentanyl	↑ Fentanyl	Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when fentanyl is concomitantly administered with KALETRA.

Antiarrhythmics: Amiodarone, Bepridil, Dronedarone (see **CONTRAINDICATIONS**) Lidocaine (systemic), and Quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA, if available.
Antiarrhythmics: Digoxin	↑ Digoxin	A literature report has shown that coadministration of ritonavir (300mg 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: Abemaciclib Apalutamide Dasatinib Encorafenib Ibrutinib Ivosidenib Neratinib Nilotinib Venetoclax Vincristine Vinblastine	↑ Anticancer agents	Concentrations of these anticancer agents may be increased when co-administered with lopinavir/ritonavir (KALETRA) resulting in the potential for increased adverse events usually associated with these anticancer agents, some of which may be serious. Coadministration of venetoclax or ibrutinib with lopinavir/ritonavir could increase venetoclax or ibrutinib exposure potentially resulting in a serious risk of tumor lysis syndrome. Coadministration of encorafenib or ivosidenib with lopinavir/ritonavir could increase encorafenib or ivosidenib exposure potentially increasing the risk of serious adverse events such as QT interval prolongation. For venetoclax, encorafenib, ibrutinib, ivosidenib, nilotinib and dasatinib, refer to their prescribing information for dosing instructions. Coadministration of apalutamide is contraindicated with Kaletra since apalutamide may decrease exposure of Kaletra with potential loss of virologic response. In addition, co-administration of apalutamide and Kaletra may lead to increased exposure of apalutamide resulting in increased potential for adverse events including seizure.
Anticoagulants: Rivaroxaban	↑ Rivaroxaban	Co-administration of rivaroxaban and KALETRA may increase rivaroxaban exposure which may increase the risk of bleeding.
Anticoagulants: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, Phenobarbital, Phenytoin	↓ Lopinavir ↓ Phenytoin	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly. KALETRA should not be administered once daily in combination with phenobarbital, phenytoin or carbamazepine. In addition, co-administration of phenytoin and KALETRA resulted in moderate decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with KALETRA.
Anticonvulsants: Lamotrigine* Valproate*	↓ Lamotrigine ↓ Valproate	Co-administration of KALETRA and either of these drugs was associated with reduction in exposure of the anticonvulsant; 50% reduction in lamotrigine exposure has been reported. Use with caution. A dose increase of the anticonvulsant may be needed when coadministered with KALETRA and therapeutic concentration monitoring for the anticonvulsant may be indicated, particularly during dosage adjustments.
Antidepressant: Bupropion	↓ Bupropion ↓ Active metabolite, hydroxybupropion	Concurrent administration of bupropion with KALETRA will decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion). Patients receiving KALETRA and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: Trazodone	↑ Trazodone	Concomitant use of trazodone and KALETRA may increase concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Antigout: Colchicine	↑ Colchicine	Concentrations of colchicine are expected to increase when coadministered with KALETRA. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and ritonavir (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**). Refer to the colchicine label for prescribing information.

Anti-infective: Clarithromycin	↑ Clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: Ketoconazole*, Itraconazole, Voriconazole	↑ Ketoconazole ↑ Itraconazole ↓ Voriconazole	High doses of ketoconazole or itraconazole (> 200 mg/day) are not recommended. Co-administration of voriconazole with KALETRA has not been studied. A study has shown that co-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 should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
Antimycobacterial: Rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
Antimycobacterial: Rifampin	↓ Lopinavir	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. A study evaluated combination of rifampin 600 mg QD, with KALETRA 800/200 mg BID or KALETRA 400/100 mg + ritonavir 300 mg BID. Pharmacokinetic and safety results from this study do not allow for a dose recommendation. Nine subjects (28%) experienced a ≥ grade 2 increase in ALT/AST, of which seven (21%) prematurely discontinued study per protocol. Based on the study design, it is not possible to determine whether the frequency or magnitude of the ALT/AST elevations observed is higher than what would be seen with rifampin alone. (See **CLINICAL PHARMACOLOGY** for magnitude of interaction – Table 5).
Antimycobacterial: Bedaquiline	↑ Bedaquiline	In a healthy volunteer drug interaction study of 400 mg single dose bedaquiline and lopinavir/ritonavir 400/100 mg twice daily for 24 days, bedaquiline exposures (AUC) were increased by 22%. Bedaquiline must be used cautiously with lopinavir/ritonavir, only if the benefit of co-administration outweighs the risk (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).
Antimycobacterial: Delamanid	↑ Delamanid	In a healthy volunteer drug interaction study of delamanid 100 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily for 14 days, exposures of delamanid and a delamanid metabolite, DM-6705, were slightly increased. Due to the risk of QTc prolongation associated with DM-6705, if co-administration of delamanid with lopinavir/ritonavir is considered necessary, frequent ECG monitoring throughout the full delamanid treatment period is recommended (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).
Antiparasitic: Atovaquone	↓ Atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Antipsychotics: Quetiapine	↑ Quetiapine	Due to CYP3A inhibition by lopinavir/ritonavir, concentrations of quetiapine are expected to increase. Refer to quetiapine prescribing information for dosing instructions (see **WARNINGS AND PRECAUTIONS**).
Calcium Channel Blockers, Dihydropyridine: e.g., Felodipine, Nifedipine, Nicardipine	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroids: Dexamethasone	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.

Corticosteroids: Inhaled, injectable, or intranasal fluticasone propionate, budesonide, triamcinolone		Concomitant use of KALETRA and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Consider alternatives to fluticasone propionate, budesonide, and injectable triamcinolone, particularly for long-term use (See **WARNINGS AND PRECAUTIONS: Drug Interactions**).
Disulfiram/Metronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
PDE5 inhibitors: Avanafil, Sildenafil, Tadalafil, Vardenafil	↑ Avanafil ↑ Sildenafil ↑ Tadalafil ↑ Vardenafil	Do not use KALETRA with avanafil because a safe and effective avanafil dosage regimen has not been established. Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving KALETRA. Co-administration of KALETRA with these drugs is expected to substantially increase their concentrations and may result in an increase in associated adverse reactions including hypotension, syncope, visual changes and prolonged erection. 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 **WARNINGS AND PRECAUTIONS: *Drug Interactions***). Concomitant use of sildenafil with KALETRA is contraindicated in pulmonary arterial hypertension (PAH) patients (see **CONTRAINDICATIONS**). Use tadalafil with caution at reduced doses of no more than 10 mg every 72 hours with increased monitoring for adverse events (see **WARNINGS AND PRECAUTIONS: Drug Interactions**). When tadalafil is administered in patients with pulmonary arterial hypertension who are receiving lopinavir/ritonavir, refer to the tadalafil label for prescribing information. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events (see **WARNINGS AND PRECAUTIONS: Drug Interactions**).
GnRH Receptor Antagonists: Elagolix		Coadministration of elagolix with lopinavir/ritonavir could increase elagolix exposure through inhibition of OATP, CYP 3A, and P-gp. Known serious adverse events for elagolix include suicidal ideation and hepatic transaminase elevations. In addition, elagolix is a weak/moderate inducer of CYP3A, which may decrease exposure of lopinavir/ritonavir. Refer to the elagolix label for dosing information with strong CYP-3A4 inhibitors.
Kinase Inhibitors (also see anticancer agents above): Fostamatinib		Coadministration of fostamatinib with lopinavir/ritonavir could increase fostamatinib metabolite R406 exposure resulting in dose-related adverse events such as hepatotoxicity and neutropenia.
Herbal Products: St Johns wort	↓ Lopinavir	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 KALETRA. This effect may be due to an induction of CYP3A4 and may result in the loss of therapeutic effect and development of resistance (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS: *Drug Interactions***).
HMG-CoA Reductase Inhibitors: Lovastatin, Simvastatin	↑ Lovastatin ↑ Simvastatin	Lovastatin and simvastatin are expected to have markedly increased plasma concentrations when co-administered with KALETRA. Since increase concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolosis, the combination of these drugs with KALETRA is contraindicated (see **CONTRAINDICATIONS**).
HMG-CoA Reductase Inhibitors: Atorvastatin* Rosuvastatin	↑ Atorvastatin ↑ Rosuvastatin	Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Lomitapide		Lomitapide is a sensitive substrate for CYP3A4 metabolism. CYP3A4 inhibitors increase the exposure of lomitapide, with strong inhibitors increasing exposure approximately 27-fold. Concomitant use of moderate or strong CYP3A4 inhibitors with lomitapide is contraindicated.

Immunosuppressants: Cyclosporine, Tacrolimus, Rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Inhaled Steroid: Fluticasone	↑ Fluticasone	Concomitant use of fluticasone propionate and KALETRA may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during post-marketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Co-administration of fluticasone propionate and KALETRA is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effect
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA. Monitoring plasma concentrations of methadone is recommended.
Oral Contraceptive: Ethinyl estradiol*	↓ Ethinyl estradiol	Because contraceptive steroid concentrations may be altered when KALETRA is co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.
Vasodilating Agents: Bosentan	↑ Bosentan	Co-administration of bosentan and KALETRA increased steady-state bosentan maximum concentrations (C_{max}) and area-under-the-curve (AUC) by 6-fold and 5-fold, respectively. Refer to the bosentan label for prescribing information.
* See **CLINICAL PHARMACOLOGY** for Magnitude of Interaction - Table 5 and Table 6.		

Other Drugs

Drug interaction studies reveal no clinically significant interaction with KALETRA and desipramine (CYP2D6 probe), pravastatin, stavudine, lamivudine, omeprazole or ranitidine (See **CLINICAL PHARMACOLOGY**: Tables 4 and 5).

Clinical studies show no clinically significant interaction between KALETRA and raltegravir.

Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

PREGNANCY AND LACTATION

Pregnancy, Fertility and Reproduction

Human Data

Risk Summary

Lopinavir/ritonavir has been evaluated in 3,366 women during pregnancy.
Available human data suggest that lopinavir/ritonavir does not increase the risk of overall major birth defects compared to the background rate. Lopinavir/ritonavir can be used during pregnancy if clinically needed.

Antiretroviral Pregnancy Registry

In post-marketing surveillance through the Antiretroviral Pregnancy Registry, established since January 1989, no increased risk of birth defects has been reported among over 1000 women exposed to lopinavir/ritonavir in the first trimester. The prevalence of birth defects after any trimester exposure to lopinavir is comparable to the prevalence observed in the general population. No pattern of birth defects suggestive of a common etiology was seen.

Clinical Trials

In an open-label pharmacokinetic study, 12 HIV-infected pregnant women who were less than 20 weeks of gestation and on combination antiretroviral therapy initially received lopinavir/ritonavir 400 mg/100 mg (two 200/50 mg tablets) twice daily up to a gestational age of 30 weeks. At 30 weeks age of gestation, the dose was increased to 500/125 mg (two 200/50 mg tablets plus one 100/25 mg tablet) twice daily until subjects were 2 weeks postpartum (see **CLINICAL PHARMACOLOGY - Special Populations - Pregnancy**). Except for two reported TEAEs (anemia in a zidovudine and penicillin-treated patient, and H1N1 influenza), no other serious adverse events and deaths were reported. All subjects tolerated the dose increase, with no premature discontinuations.

In another open-label pharmacokinetic study, 19 HIV-infected pregnant women received lopinavir/ritonavir 400/100 mg twice daily as part of combination antiretroviral therapy during pregnancy from before conception (see **CLINICAL PHARMACOLOGY - Special Populations - Pregnancy**). Laboratory abnormalities included 2 cases of Grade 3 increases in ALT. Pregnancy related events included 1 case of preeclampsia, 6 preterm deliveries, 7 cases of low birth weight infants (<2500 grams), and 2 stillbirths. No deaths, serious adverse events or discontinuations due to adverse events were reported. Seventeen of 19 patients had HIV RNA < 50 copies/mL at delivery.

Animal Data

Lopinavir in combination with ritonavir at a 2 to 1 ratio produced no effects on fertility in male and female rats at maximum achievable doses producing drug exposures which were comparable to or slightly less than those achieved with the recommended therapeutic dose. levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in

rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were 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 twice-daily).

Nursing Mothers

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving KALETRA. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk.

ADVERSE REACTIONS

Adults

Treatment-Emergent Adverse Reactions

The safety of KALETRA has been investigated in over 2,600 patients in Phase II-IV clinical trials, of which more than 700 have received a dose of 800/200 mg (6 capsules or 4 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies, KALETRA was used in combination with efavirenz or nevirapine.

Commonly reported adverse reactions to KALETRA during clinical trials included diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. Diarrhea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridemia and hypercholesterolemia may occur later.

The following have been identified as adverse reactions of moderate or severe intensity (Table 14):

Table 14. Treatment-Emergent Adverse Reactions of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult Patients Receiving KALETRA in Combined Phase II-IV Studies (N= 2,612)

System Organ Class (SOC) and Adverse Reaction	n	%
BLOOD AND LYMPHATIC SYTEM DISORDERS		
anemia*	54	2.067
leukopenia and neutropenia*	44	1.685
lymphadenopathy*	35	1.340
CARDIAC DISORDERS		
atherosclerosis such as myocardial infarction*	10	0.383
atrioventricular block*	3	0.115
tricuspid valve incompetence*	3	0.115
EAR AND LABYRINTH DISORDERS		
vertigo*	7	0.268
tinnitus	6	0.230
ENDOCRINE DISORDERS		
hypogonadism*	16	0.785[1]
EYE DISORDERS		
visual Impairment*	8	0.306
GASTROINTESTINAL DISORDERS		
diarrhea*	510	19.525
nausea	269	10.299
vomiting*	177	6.776
abdominal pain (upper and lower)*	160	6.126
gastroenteritis and colitis*	66	2.527
dyspepsia	53	2.029
pancreatitis*	45	1.723
Gastroesophageal Reflux Disease (GERD)*	40	1.531
hemorrhoids	39	1.493
flatulence	36	1.378
abdominal distension	34	1.302
constipation*	26	0.995
stomatitis and oral ulcers*	24	0.919
duodenitis and gastritis*	20	0.766
gastrointestinal hemorrhage including rectal hemorrhage*	13	0.498
dry mouth	9	0.345
gastrointestinal ulcer*	6	0.230

fecal incontinence	5	0.191
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
fatigue including asthenia*	198	7.580
HEPATOBILIARY DISORDERS		
hepatitis including AST, ALT, and GGT increases*	91	3.484
hepatomegaly	5	0.191
cholangitis	3	0.115
hepatic steatosis	3	0.115
IMMUNE SYSTEM DISORDERS		
hypersensitivity including urticaria and angioedema*	70	2.680
immune reconstitution syndrome	3	0.115
INFECTIONS AND INFESTATIONS		
upper respiratory tract infection*	363	13.897
lower respiratory tract infection*	202	7.734
skin infections including cellulitis, folliculitis, and furuncle*	86	3.292
METABOLISM AND NUTRITION DISORDERS		
hypercholesterolemia*	192	7.351
hypertriglyceridemia*	161	6.164
weight decreased*	61	2.335
decreased appetite	52	1.991
blood glucose disorders including diabetes mellitus*	30	1.149
weight increased*	20	0.766
lactic acidosis*	11	0.421
increased appetite	5	0.191
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
musculoskeletal pain including arthralgia and back pain*	166	6.355
myalgia*	46	1.761
muscle disorders such as weakness and spasms*	34	1.302
rhabdomyolysis*	18	0.689
osteonecrosis	3	0.115
NERVOUS SYSTEM DISORDERS		
headache including migraine*	165	6.317
insomnia*	99	3.790
neuropathy and peripheral neuropathy*	51	1.953
dizziness*	45	1.723
ageusia*	19	0.727
convulsion*	9	0.345
tremor*	9	0.345
cerebral vascular event*	6	0.230
PSYCHIATRIC DISORDERS		
anxiety*	101	3.867
abnormal dreams*	19	0.727
libido decreased	19	0.727
RENAL AND URINARY DISORDERS		
renal failure*	31	1.187
hematuria*	20	0.766
nephritis*	3	0.115
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
erectile dysfunction*	34	1.668[1]
menstrual disorders - amenorrhea, menorrhagia*	10	1.742[2]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
rash including maculopapular rash*	99	3.790
dermatitis/rash including eczema and seborrheic dermatitis*	50	1.914
night sweats*	42	1.608
pruritus*	29	1.110
alopecia	10	0.383
capillaritis and vasculitis*	3	0.115
VASCULAR DISORDERS		
hypertension*	47	1.799
deep vein thrombosis*	17	0.651

*Represents a medical concept including several similar MedDRA PTs
1. Percentage of male population (N=2,038)
2. Percentage of female population (N=574)

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 15 and Table 16.

Table 15. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-naive Patients

		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	NA	NA	10%	NA	NA
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%	NA	NA
Lipase	> 2 x ULN	NA	NA	NA	NA	NA	3%	5%
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).

Table 16. 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 BID + NVP + NRTIs (N = 148)**	**Investigator-selected protease inhibitor(s) + NVP + NRTIs (N = 140)**	**KALETRA BID + NNRTI + NRTIs (N = 127)**	**KALETRA 800/200 mg once daily + NRTIs (N = 300)**	**KALETRA 400/100 mg 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[4]	> 180 U/L	5%	11%	8%	3%	2%
SGPT/ALT[4]	> 215 U/L	6%	13%	10%	2%	2%
GGT	> 300 U/L	N/A	N/A	29%	NA	NA
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	> 2 x ULN	NA	NA	NA	4%	1%
Creatine Phosphokinase	> 4 x ULN	NA	NA	NA	4%	5%
Chemistry	**Low**					
Calculated Creatinine Clearance	< 50 mL/min	NA	NA	NA	3%	3%
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%
Hemoglobin	< 80 g/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 400/100 mg BID (n = 29) or 533/133 mg BID (n = 28) for 84 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.

3 Includes clinical laboratory data from patients receiving 400/100 mg BID (n = 36) or 400/200 mg BID (n = 34) for 144 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.

4 Criterion for Study 802 was > 5x ULN (AST/ALT).

Pediatrics

Treatment-emergent Adverse Events

KALETRA has been studied in 100 pediatric 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 diarrhea were the most commonly reported drug related adverse events of any severity in pediatric patients treated with combination therapy including KALETRA for up to 48 weeks in Study M98-940. 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 ≥ 2% of children enrolled.

Laboratory Abnormalities

The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 17.

Table 17. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients

Variable	Limit[1]	KALETRA BID+ RTIs (N = 100)
Chemistry	**High**	
Sodium	> 149 mEq/L	3%
Total Bilirubin	≥ 3.0 x ULN	3%
SGOT/AST	> 180 U/L	8%
SGPT/ALT	> 215 U/L	7%
Total Cholesterol	> 300 mg/dL	3%
Amylase	> 2.5 x ULN	7%[2]
Chemistry	**Low**	
Sodium	< 130 mEq/L	3%
Hematology	**Low**	
Platelet Count	< 50 x 10^9/L	4%
Neutrophils	< 0.40 x 10^9/L	2%

1 ULN = upper limit of the normal range.
2 Subjects with Grade 3-4 amylase confirmed by elevations in pancreatic amylase.

Post Marketing Experience

Hepatobiliary disorders: Hepatitis has been reported in patients on KALETRA therapy.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme have been reported.

Cardiac disorders: Bradyarrhythmia has been reported.

Renal and urinary disorders: Nephrolithiasis

Metabolic Parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE

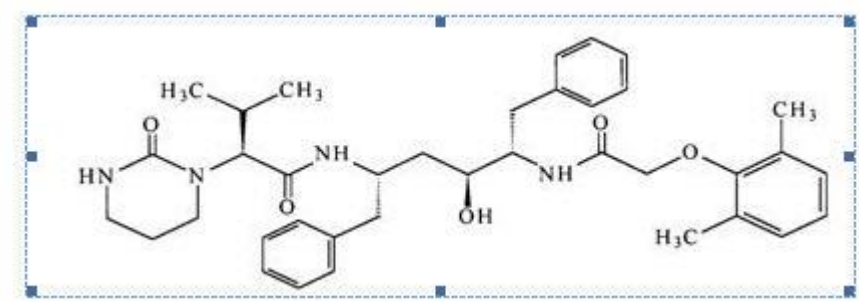
Overdoses with KALETRA oral solution have been reported. One of these reports described fatal cardiogenic shock in a 2.1 kg infant who received a single dose of 6.5 mL of KALETRA oral solution (520 mg lopinavir, approximately 10-fold above the recommended lopinavir dose) nine days prior. The following events have been reported in association with unintended overdoses in preterm neonates: complete AV block, cardiomyopathy, lactic acidosis, and acute renal failure. Healthcare professionals should be aware that KALETRA oral solution is highly concentrated and contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v), and therefore, should pay special attention to accurate calculation of the dose of KALETRA, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors and overdose. This is especially important for infants and young children (see **DESCRIPTION, DOSAGE AND ADMINISTRATION,** and **WARNINGS AND PRECAUTIONS-Serious Toxicity in Neonates** and **Pediatric Use**).

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. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since KALETRA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug. However, dialysis can remove both alcohol and propylene glycol in the case of overdose with KALETRA oral solution.

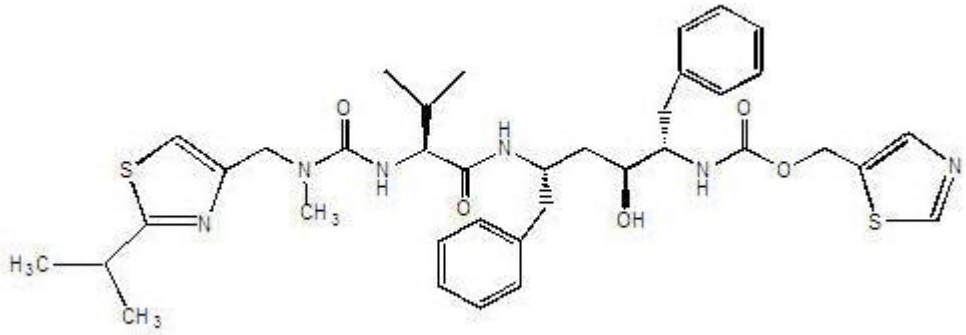
DESCRIPTION

KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV proteases. As co-formulated in KALETRA, ritonavir inhibits the cytochrome P450 3A (CYP3A)-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

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



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:



KALETRA film coated tablets are available for oral administration in a strength of 200 mg of lopinavir and 50 mg of ritonavir or 100 mg of lopinavir and 25 mg of ritonavir with the following inactive ingredients: copovidone, sorbitan laurate, colloidal anhydrous silica and sodium stearyl fumarate. The following are the ingredients in the film coating for the 200/50 mg tablet: hypromellose, titanium dioxide, macrogols type 400, hydroxypropyl cellulose, talc, colloidal anhydrous silica, macrogols type 3350, yellow ferric oxide E172, and polysorbate 80. The following are the ingredients in the film coating for the 100/25 mg tablet: polyvinyl alcohol, titanium dioxide, talc, macrogols type 3350, yellow ferric oxide E172.

KALETRA oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: Alcohol, high fructose corn syrup, propylene glycol, water, glycerin, povidone, Magnasweet-110 flavor, natural and artificial vanilla flavor, polyoxyl 40 hydrogenated castor oil, artificial cotton candy flavor, acesulfame potassium, saccharin sodium, sodium chloride, peppermint oil, sodium citrate, citric acid, and menthol.
KALETRA oral solution contains 42.4% alcohol (v/v) and 15.3% propylene glycol (w/v).

DOSAGE AND ADMINISTRATION

KALETRA tablets may be taken with or without food.

KALETRA oral solution must be taken with food.

KALETRA tablets should be swallowed whole and not chewed, broken, or crushed.

The recommended oral dose of KALETRA is as follows: (Please also refer to **INDICATIONS AND USAGE** and **ADVERSE REACTIONS**)

Adults

The recommended oral dose of KALETRA is 400/100 mg (two 200/50 mg tablets or 5 ml oral solution) twice daily. KALETRA may also be administered as 800/200 mg (four 200/50 mg tablets or 10 ml oral solution) 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 **DESCRIPTION OF CLINICAL STUDIES**).

KALETRA should not be administered once daily in combination with carbamazepine, phenobarbital, or phenytoin (see **DRUG INTERACTIONS**).

Concomitant Therapy

Efavirenz, nevirapine, amprenavir or nelfinavir

- KALETRA 400/100 mg tablets can be used twice-daily in combination with these drugs with no dose adjustment in antiretroviral-naïve patients.
- A dose increase of KALETRA tablets to 500/125 mg (two 200/50 mg tablets and one 100/25 mg tablet) twice-daily may be considered when used in combination with efavirenz, nevirapine, amprenavir without ritonavir or nelfinavir in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **DRUG INTERACTIONS**).

- A dose increase of KALETRA oral solution to 533/133 mg (6.5 mL) twice-daily taken with food is recommended when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence) (see **DRUG INTERACTIONS**).

KALETRA should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

Dosing During Pregnancy and the Postpartum Period

Tablets

- Administer 400/100 mg of KALETRA twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions. Once daily KALTERA dosing is not recommended in pregnancy and postpartum.
- There are insufficient data to recommend dosing in pregnant women with any documented lopinavir-associated resistance substitutions.
- No dosage adjustment of KALTERA is required for patients during the postpartum period.

Pediatric Patients

KALETRA tablets and oral solution should not be administered once daily in pediatric patients < 18 years of age. The adult dose (400/100 mg BD) may be used in children > 12 years of age.

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 potentially lethal toxicity from these excipients (see **DESCRIPTION**, **WARNINGS AND PRECAUTIONS**, AND **OVERDOSAGE**).

In children 6 months to 12 years of age, the recommended dosage of KALETRA oral solution is 12/3 mg/kg for those 7 to < 15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice-daily taken with food, up to a maximum dose of 400/100 mg in children > 40 kg (5.0 mL or 2 tablets) twice-daily. **It is preferred that the prescriber calculate the appropriate milligram dose for each individual child ≤ 12 years old and determine the corresponding volume of solution or number of tablets**. However, as an alternative, the following table contains dosing guidelines for KALETRA oral solution or 100/25 mg tablet based on body weight. When possible, dose of the oral solution should be administered using a calibrated dosing syringe.

Before prescribing KALETRA 100/25 mg tablets, children should be assessed for the ability to swallow intact tablets. If a child is unable to reliably swallow a KALETRA tablet, the KALETRA oral solution formulation should be prescribed.

Weight (kg)	**Dose (mg/kg)***	**Volume of Oral Solution BID (80 mg lopinavir/20 mg ritonavir per mL)**	**Number of 100/25 mg Tablets twice-daily**
Without nevirapine, efavirenz or amprenavir			
7 to < 15 kg	12 mg/kg BID†		
7 to 10 kg		1.25 mL	Tablets are not recommended. Use oral solution
> 10 to < 15 kg		1.75 mL	Tablets are not recommended. Use oral solution
15 to 40 kg	10 mg/kg BID		
15 to 20 kg		2.25 mL	2#
> 20 to 25 kg		2.75 mL	2#
> 25 to 30 kg		3.5 mL	3
> 30 to 35 kg		4.0 mL	3
> 35 to 40 kg		4.75 mL	4 (or two 200/50 mg tablets)
> 40 kg	400 mg BID	5 mL	4 (or two 200/50 mg tablets)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
† Dose is also approximately equivalent to lopinavir/ritonavir 230/57.5 mg/m^2.
# Alternatively one 200/50 mg tablets may be used for this dose in those patients who can swallow the larger tablet.
Note: Use adult dosage recommendation for children > 12 years of age.

Concomitant Therapy: Efavirenz, nevirapine or amprenavir

A dose increase of KALETRA is needed when co-administered with efavirenz, nevirapine or amprenavir in children 6 months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). For oral solution, a dose increase to 13/3.25 mg/kg for those 7 to < 15 kg and 11/2.75 mg/kg for those 15 to 45 kg (approximately equivalent to 300/75 mg/m^2) twice-daily taken with food, up to a maximum dose of 533/133 mg in children > 45 kg twice-daily is recommended. The following table contains dosing guidelines for KALETRA oral solution and 100/25 mg tablet based on body weight, when used in combination with efavirenz, nevirapine or amprenavir in children (see **CLINICAL PHARMACOLOGY -** Drug-drug Interactions Table 5 and/or **DRUG INTERACTIONS** Table 13).

Weight (kg)	**Dose (mg/kg)***	**Volume of Oral Solution BID (80 mg lopinavir/20 mg ritonavir per mL)**	**Number of 100/25 mg Tablets twice-daily**
With nevirapine, efavirenz or amprenavir			
7 to < 15 kg	13 mg/kg BID†		
7 to 10 kg		1.5 mL	Tablets are not recommended. Use oral solution

> 10 to < 15 kg		2.0 mL	Tablets are not recommended. Use oral solution
15 to 45 kg	11 mg/kg BID†		
15 to 20 kg		2.5 mL	2#
> 20 to 25 kg		3.25 mL	3
> 25 to 30 kg		4.0 mL	3
> 30 to 35 kg		4.5 mL	4 (or two 200/50 mg tablets)
> 35 to 40 kg		5.0 mL	4 (or two 200/50 mg tablets)
> 40 to 45 kg		5.75 mL	4 (or two 200/50 mg tablets)
> 45 kg	500 mg BID	6.5 mL	5

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
† Dose is also approximately equivalent to lopinavir/ritonavir 300/75 mg/m^2.
# Alternatively one 200/50 mg tablet may be used for this dose in those patients who can swallow the larger tablet.
Note: Use adult dosage recommendation for children > 12 years of age.

Use of Oral Solution with a feeding tube

The prescribed dose of KALETRA oral solution can be administered via a feeding tube. Follow the instructions for the feeding tube to administer the medicine. Products containing alcohol, like KALETRA, are not recommended for use with polyurethane feeding tubes due to potential incompatibility.

HOW SUPPLIED

1. KALETRA Tablets, 200 mg lopinavir / 50 mg ritonavir
KALETRA (lopinavir/ritonavir) 200/50 mg tablets are yellow film-coated ovaloid tablets debossed with the corporate **Abbott "A" logo** and the Abbo-Code KA.

Bottles of 120 tablets ….…… (NDC 0074-6799-22)

Recommended Storage

Store KALETRA film-coated tablets at or below 30^{0}C. Dispense in original container. For patient use: exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.

2. KALETRA Tablets, 100 mg lopinavir / 25 mg ritonavir
KALETRA (lopinavir/ritonavir) 100/25 mg tablets are pale yellow film-coated ovaloid tablets debossed with the corporate **Abbott "A" logo** and the Abbo-Code KC.

Bottles of 60 tablets ….…… (NDC 0074-0522-60)

Recommended Storage

Store KALETRA film-coated tablets at or below 30^{0}C. Dispense in original container. For patient use: exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.

3. KALETRA Oral Solution
KALETRA (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL) packaged with a marked dosing cup in the following size:

160 mL bottle……(NDC 0074-3956-46)

Recommended Storage

Store KALETRA oral solution at 36° F-46° F (2° C-8° C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 77° F (25° C), oral solution should be used within 2 months.

Information for Patients

A Patient Information Leaflet (PIL) for KALETRA is available for patient information.

Patients and/or their care providers should pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or underdose of KALETRA.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that KALETRA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV to others through sexual contact.

KALETRA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

KALETRA tablets can be taken at the same time as didanosine without food. Patients taking didanosine should take didanosine one hour before or two hours after KALETRA oral solution.

Patients receiving avanafil, sildenafil, tadalafil, or vardenafil should be advised that they may be at an increased risk of associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with KALETRA.

KALETRA tablets may be taken with or without food. KALETRA oral solution should be taken with food to enhance absorption.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

AbbVie Inc

North Chicago, IL 60064, U.S.A.

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