

NDA 21-226/S-020

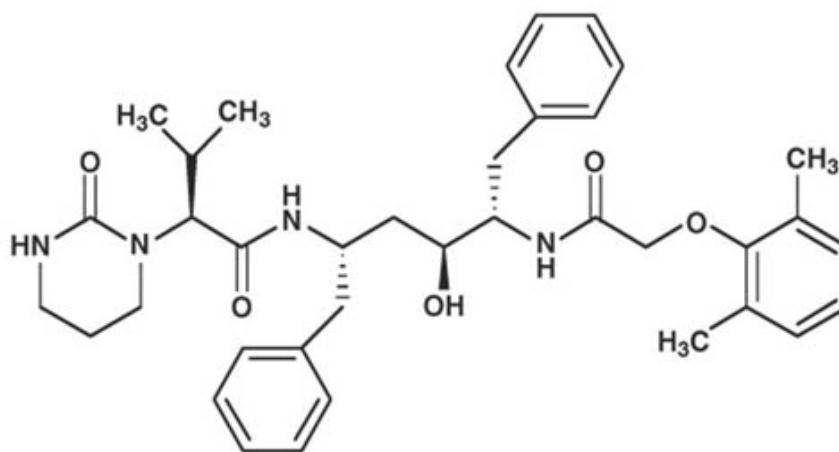
Page 3

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

DESCRIPTION

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

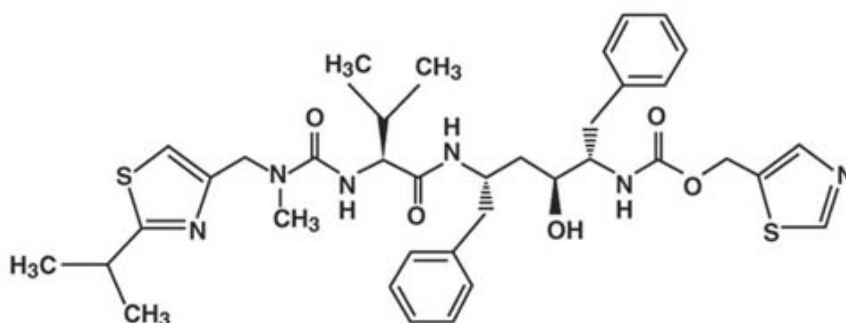
Lopinavir is chemically designated as [1S-[1R*, (R*), 3R*, 4R*]]-N-[4-[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir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



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:

NDA 21-226/S-020

Page 4



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

KALETRA capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

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

KALETRA oral solution contains 42.4% alcohol (v/v).

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.

NDA 21-226/S-020

Page 5

Antiviral Activity

The 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}) values of lopinavir against five different HIV-1 subtype B laboratory strains ranged from 10-27 nM (0.006-0.017 $\mu\text{g/mL}$, 1 $\mu\text{g/mL}$ = 1.6 μM) and ranged from 4-11 nM (0.003-0.007 $\mu\text{g/mL}$) against several HIV-1 subtype B clinical isolates ($n = 6$). In the presence of 50% human serum, the mean EC_{50} values of lopinavir against these five HIV-1 laboratory strains ranged from 65-289 nM (0.04-0.18 $\mu\text{g/mL}$), representing a 7- to 11-fold attenuation. Combination antiviral drug activity studies with lopinavir in cell cultures demonstrated additive to antagonistic activity with nelfinavir and additive to synergistic activity with amprenavir, atazanavir, indinavir, saquinavir and tipranavir. The EC_{50} values of lopinavir against three different HIV-2 strains ranged from 12-180 nM (0.008-113 $\mu\text{g/mL}$).

Resistance

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

The selection of resistance to KALETRA in antiretroviral treatment-naive patients has not yet been characterized. In a Phase III study of 653 antiretroviral treatment-naive patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV >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%). The selection of resistance to KALETRA in antiretroviral treatment-naive pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

NDA 21-226/S-020

Page 6

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-naïve 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 (indinavir, nelfinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, ritonavir, and saquinavir). 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.

NDA 21-226/S-020
Page 7

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 KALETRA¹

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.

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 >1,000 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

NDA 21-226/S-020

Page 8

nucleoside reverse transcriptase inhibitors (NRTIs). The EC₅₀ values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold the wild-type EC₅₀ value. Fifty-five percent (31/56) of these baseline isolates displayed >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 2.

Table 2. HIV-RNA Response at Week 48 by Baseline Lopinavir Susceptibility¹

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.

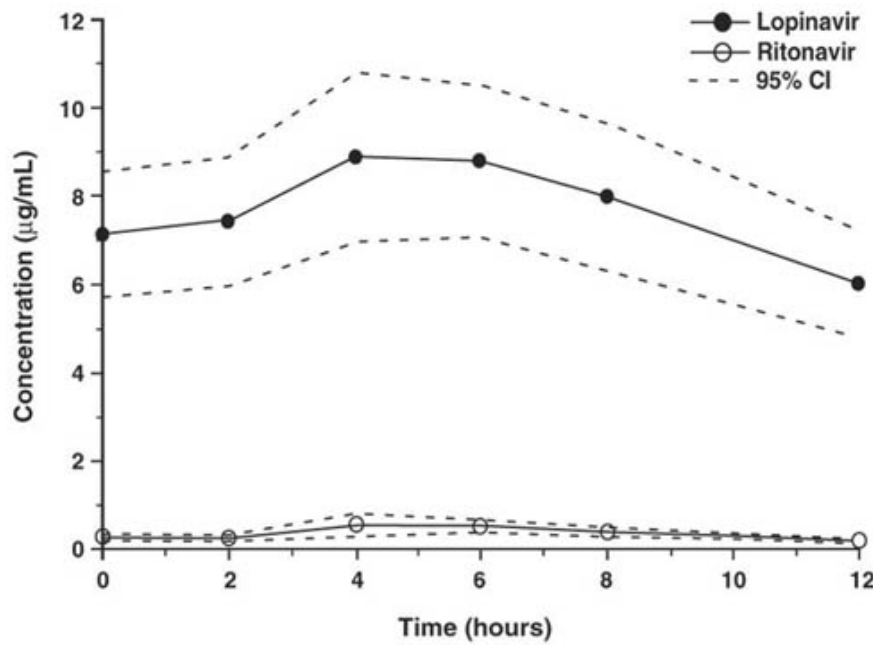
Pharmacokinetics

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 EC₅₀ of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of KALETRA is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 400/100 mg twice-daily with food for 3 weeks from a pharmacokinetic study in HIV-infected adult subjects (n = 19).

NDA 21-226/S-020
Page 9

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 = 19), multiple dosing with 400/100 mg KALETRA twice-daily with food for 3 weeks produced a mean $\pm$ SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 $\mu\text{g/mL}$, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 $\mu\text{g/mL}$ and minimum concentration within a dosing interval was 5.5 ± 2.7 $\mu\text{g/mL}$. Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 $\mu\text{g} \cdot \text{h/mL}$. 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.

NDA 21-226/S-020

Page 10

Effects of Food on Oral Absorption

Administration of a single 400/100 mg dose of KALETRA capsules with a moderate fat meal (500-682 kcal, 23 to 25% calories from fat) was associated with a mean increase of 48 and 23% in lopinavir AUC and C_{max} , respectively, relative to fasting. For KALETRA oral solution, the corresponding increases in lopinavir AUC and C_{max} were 80 and 54%, respectively. Relative to fasting, administration of KALETRA with a high fat meal (872 kcal, 56% from fat) increased lopinavir AUC and C_{max} by 97 and 43%, respectively, for capsules, and 130 and 56%, respectively, for oral solution. To enhance bioavailability and minimize pharmacokinetic variability KALETRA 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

NDA 21-226/S-020

Page 11

decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination

Following a 400/100 mg ¹⁴C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ¹⁴C-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 ± 5.75 L/hr (mean ± SD, n = 19).

Once Daily Dosing

The pharmacokinetics of once daily KALETRA have been evaluated in HIV-infected subjects naïve to antiretroviral treatment. KALETRA 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once daily regimen. Multiple dosing of 800/200 mg KALETRA once-daily for 4 weeks with food (n = 24) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 11.8 ± 3.7 µg/mL, occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 3.2 ± 2.1 µg/mL and minimum concentration within a dosing interval was 1.7 ± 1.6 µg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 154.1 ± 61.4 µg• h/mL.

Special Populations

Gender, Race and Age

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

NDA 21-226/S-020

Page 12

Pediatric Patients

The pharmacokinetics of KALETRA 300/75 mg/m² twice-daily and 230/57.5 mg/m² 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/m² twice-daily regimen without nevirapine and the 300/75 mg/m² 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). KALETRA once-daily has not been evaluated in pediatric patients.

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 230/57.5 mg/m² 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/m² 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

NDA 21-226/S-020

Page 13

KALETRA to subjects with hepatic impairment. KALETRA has not been studied in patients with severe hepatic impairment (see **PRECAUTIONS**).

Drug-drug Interactions

See also **CONTRAINDICATIONS** , **WARNINGS** and **PRECAUTIONS – 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 3 (effect of other drugs on lopinavir) and Table 4 (effect of KALETRA on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the

NDA 21-226/S-020
Page 14

table footnotes. For information regarding clinical recommendations, see Table 11 in **PRECAUTIONS**.

Table 3. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug (See PRECAUTIONS – Table 11 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (in combination with Co-administered drug-/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C _{max}	AUC	C _{min}
Amprenavir	750 BID, 10 d	400/100 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 BID, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz ¹	600 QHS, 9 d	400/100 BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
Fosamprenavir ²	700 BID plus ritonavir 100 BID, 14 d	400/100 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 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 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 BID, steady-state	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	(> 1 yr) 300/75 mg/m ² 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)
	40 QD, 5 d	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 BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 QD, 10 d	400/100 BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
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)
	150 single dose	800/200 tablet QD, 10 d	10	0.97 (0.95, 1.00)	0.95 (0.91, 0.99)	0.82 (0.74, 0.91)

NDA 21-226/S-020

Page 15

Rifampin	600 QD, 10 d	400/100 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 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 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 KALETRA and rifampin is not recommended. (See PRECAUTIONS – Table 10 and Table 11)						
Ritonavir ³	100 BID, 3-4 wk	400/100 BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir ⁷	300 mg QD, 14 d	400/100 BID, 14 d	24	NC [†]	NC [†]	NC [†]
Tipranavir/ritonavir ³	500/200 mg BID (28 doses)	400/100 capsule BID (27 doses)	21 69	0.53 (0.40, 0.69) ⁸	0.45 (0.32, 0.63) ⁸	0.30 (0.17, 0.51) ⁸ 0.48 (0.40, 0.58) ⁹

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.

8 Intensive PK analysis.

9 Drug levels obtained at 8-16 hrs post-dose.

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

† NC = No change.

Table 4. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA (See PRECAUTIONS – Table 11 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (in combination with KALETRA/alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C _{max}	AUC	C _{min}
Amprenavir ¹	750 BID, 10 d combo vs. 1200 BID, 14 d alone	400/100 BID, 21 d	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)

NDA 21-226/S-020

Page 16

Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Desipramine ²	100 single dose	400/100 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 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 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 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 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 BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 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 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 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 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 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 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 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 BID, 20 d	10	6.44 (5.59, 7.41)	9.91 (8.28, 11.86)	16.54 (10.91, 25.08)
Tenofovir ⁵	300 mg QD, 14 d	400/100 BID, 14 d	24	NC [†]	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

NDA 21-226/S-020

Page 17

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.

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection.

Once-daily administration of KALETRA is not recommended in therapy-experienced patients.

When initiating treatment with KALETRA in therapy-naïve patients, it should be noted that the incidence of diarrhea was greater for KALETRA once-daily compared to KALETRA twice-daily in Study 418 (57% vs. 35% - events of all grades and probably or possibly related to drug; 16% vs. 5% - events of at least moderate severity and probably or possibly related to drug) (see **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION**).

Description of Clinical Studies

Patients Without Prior Antiretroviral Therapy

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

Study 863 is an ongoing, randomized, double-blind, multicenter trial comparing treatment with KALETRA (400/100 mg twice-daily) plus stavudine and lamivudine versus nelfinavir (750 mg three-times-daily) plus

NDA 21-226/S-020
Page 18

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 CD₄ cell count was 259 cells/mm³ (range: 2 to 949 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.9 log₁₀ copies/mL (range: 2.6 to 6.8 log₁₀ copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 5.

Table 5. 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	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse event	4%	4%
Discontinued for other reasons ³	10%	8%

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 6.

Table 6. Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)

Baseline Viral Load (HIV-1 RNA copies/mL)	KALETRA +d4T+3TC			Nelfinavir +d4T+3TC		
	< 400 copies/mL ¹	< 50 copies/mL ²	n	< 400 copies/mL ¹	< 50 copies/mL ²	n
< 30,000	74%	71%	82	79%	72%	87
≥ 30,000 to < 100,000	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

NDA 21-226/S-020

Page 19

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

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

Study 418: KALETRA once-daily + tenofovir DF + emtricitabine compared to KALETRA twice-daily + tenofovir DF + emtricitabine

Study 418 is an ongoing, 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 190 antiretroviral treatment-naïve patients. Patients had a mean age of 39 years (range: 19 to 75), 54% were Caucasian, and 78% were male. Mean baseline CD₄ cell count was 260 cells/mm³ (range: 3 to 1006 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.8 log₁₀ copies/mL (range: 2.6 to 6.4 log₁₀ copies/mL).

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

Table 7. Outcomes of Randomized Treatment Through Week 48 (Study 418)

Outcome	KALETRA QD + TDF + FTC (n = 115)	KALETRA BID + TDF + FTC (n = 75)
Responder ¹	71%	65%
Virologic failure ²	10%	9%
Rebound	6%	5%
Never suppressed through Week 48	3%	4%
Death	0%	1%
Discontinued due to an adverse event	12%	7%
Discontinued for other reasons ³	7%	17%

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.

NDA 21-226/S-020

Page 20

Through 48 weeks of therapy, 71% in the KALETRA once-daily arm and 65% in the KALETRA twice-daily arm achieved and maintained HIV RNA < 50 copies/mL (95% confidence interval for the difference, -7.6% to 19.5%). Mean CD₄ cell count increases at Week 48 were 185 cells/mm³ for the KALETRA once-daily arm and 196 cells/mm³ for the KALETRA twice-daily arm.

Patients with Prior Antiretroviral Therapy

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

Study 888 is a randomized, open-label, multicenter trial comparing treatment with KALETRA (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 CD₄ cell count was 322 cells/mm³ (range: 10 to 1059 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.1 log₁₀ copies/mL (range: 2.6 to 6.0 log₁₀ copies/mL).

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

Table 8. 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	11%	19%
Never suppressed through Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons ³	14%	13%

NDA 21-226/S-020

Page 21

-
- 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 CD₄ cell count was 111 cells/mm³ for the KALETRA arm and 112 cells/mm³ for the investigator-selected protease inhibitor(s) arm.

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) are 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 CD₄ cell counts for patients in study 720 and study 765 were 338 (3-918) and 372 (72-807) cells/mm³, 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) log₁₀ copies/mL, respectively.

NDA 21-226/S-020

Page 22

Through 360 weeks of treatment in study 720, the proportion of patients with HIV RNA < 400 (< 50) copies/mL was 61% (59%) [n = 100]. Among patients completing 360 weeks of treatment with CD₄ cell count measurements [n=60], the mean (median) increase in CD₄ cell count was 501 (457) cells/mm³. 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 CD₄ cell count was 212 cells/mm³. Twenty-seven patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

CONTRAINDICATIONS

KALETRA is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

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 9.

Table 9. Drugs That Are Contraindicated With KALETRA

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/Hypnotics	Midazolam, Triazolam

WARNINGS

ALERT: Find out about medicines that should NOT be taken with KALETRA. This statement is included on the product's bottle label.

NDA 21-226/S-020

Page 23

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 – Table 9: Drugs That Are Contraindicated With KALETRA**, **PRECAUTIONS – Table 10: Drugs That Should Not Be Co-administered With KALETRA** and **Table 11: Established and Other Potentially Significant Drug Interactions**).

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 events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS – Drug Interactions** and the complete prescribing information for sildenafil, tadalafil, and vardenafil.)

Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also 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.

Concomitant use of KALETRA and St. John's wort (*hypericum perforatum*), or products containing St. John's wort, is not recommended. Co-administration of protease inhibitors, including KALETRA, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to loss of virologic response and possible resistance to lopinavir or to the class of protease inhibitors.

NDA 21-226/S-020

Page 24

A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures, resulting in significantly decreased serum cortisol concentrations. Concomitant use of KALETRA and fluticasone propionate is expected to produce the same effects. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and KALETRA is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects (see **PRECAUTIONS – Drug Interactions**).

Pancreatitis

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

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.

Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance

NDA 21-226/S-020

Page 25

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.

PRECAUTIONS

Hepatic Impairment and Toxicity

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased (see **CLINICAL PHARMACOLOGY – *Hepatic Impairment***). 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 postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of KALETRA treatment.

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 **Microbiology**).

NDA 21-226/S-020

Page 26

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.

Fat Redistribution

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

Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS – Table 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 **PRECAUTIONS – Table 11: Established and Other Potentially Significant Drug Interactions** for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in 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,

NDA 21-226/S-020

Page 27

cytomegalovirus, *Pneumocystis carinii* pneumonia, or tuberculosis) which may necessitate further evaluation and treatment.

Information for Patients

A statement to patients and health care providers is included on the product's bottle label: **"ALERT: Find out about medicines that should NOT be taken with KALETRA."** A Patient Package Insert (PPI) for KALETRA is available for patient information.

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.

Patients taking didanosine should take didanosine one hour before or two hours after KALETRA.

NDA 21-226/S-020

Page 28

Patients receiving 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 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.

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 **Table 11. Established and Other Potentially Significant Drug Interactions**). 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.

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. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations

NDA 21-226/S-020
Page 29

and reduce its therapeutic effect (see **Table 11. Established and Other Potentially Significant Drug Interactions**). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and not recommended for co-administration with KALETRA are included in **Table 10. Drugs That Should Not Be Co-administered With KALETRA**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 10. Drugs That Should Not Be Co-administered With KALETRA

Drug Class: Drug Name	Clinical Comment
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	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. (See Table 10 for further details).
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (<i>hypericum perforatum</i>)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 11. Established and Other Potentially 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 3 and Table 4

Concomitant Drug Class: Drug Name	Effect on Concentration of lopinavir or Concomitant Drug	Clinical Comment
<i>HIV-Antiviral Agents</i>		

NDA 21-226/S-020
Page 30

Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ Lopinavir	A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food is recommended when used in combination with efavirenz or nevirapine (see DOSAGE AND ADMINISTRATION). KALETRA should not be administered once-daily in combination with efavirenz or nevirapine. NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with KALETRA. Appropriate doses of the combination with respect to safety and efficacy have not been established.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine Nucleoside Reverse Transcriptase Inhibitor: didanosine	↑ Lopinavir	It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA (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.
HIV-Protease Inhibitor: amprenavir*	↑ Amprenavir (amprenavir 750 mg BID + KALETRA produces ↑ AUC, similar C _{max} , ↑ C _{min} , relative to amprenavir 1200 mg BID) ↓ Lopinavir	Increase KALETRA dose to 533/133 mg and decrease amprenavir dose to amprenavir 750 mg BID, when co-administered. (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY – Table 3 and Table 4). KALETRA should not be administered once-daily in combination with amprenavir. Appropriate doses of the combination of fosamprenavir and KALETRA have not been established.
HIV-Protease Inhibitor: fosamprenavir	↓ 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 4). 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	Increase KALETRA dose to 533/133 mg and decrease nelfinavir dose to 1000 mg BID, when co-administered (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY – Table 3 and Table 4). KALETRA should not be administered once-daily in combination with nelfinavir.
HIV-Protease Inhibitor: saquinavir*	↑ Saquinavir (saquinavir 800 mg BID + KALETRA produces ↑ AUC, ↑ C _{max} , ↑ C _{min} relative to saquinavir 1200 mg TID)	Decrease saquinavir dose to 800 mg BID, when co-administered with KALETRA 400/100 mg BID (see CLINICAL PHARMACOLOGY – Table 4). KALETRA once-daily has not been studied in combination with saquinavir.
HIV-Protease Inhibitor: tipranavir	↓ Lopinavir AUC and C _{min}	KALETRA should not be administered with tipranavir (500 mg twice-daily) co-administered with ritonavir (200 mg twice-daily).

NDA 21-226/S-020

Page 31

HIV-Protease Inhibitor: ritonavir*	↑ Lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
Other Agents		
Antiarrhythmics: amiodarone, bepiridil, lidocaine (systemic), and quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA, if available.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ Lopinavir	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 carbamazepine, phenobarbital, or phenytoin.
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.
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%.
Antifungals: ketoconazole*, itraconazole, voriconazole	↑ Ketoconazole ↑ Itraconazole Voriconazole effect is unknown.	No dose adjustment for patients with normal renal function is necessary. High doses of ketoconazole or itraconazole (> 200 mg/day) are not recommended. Co-administration of voriconazole with KALETRA has not been studied. However, administration of voriconazole with ritonavir 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82%. The effect of lower ritonavir doses on voriconazole is not known at this time. Until data are available, voriconazole should not be administered to patients receiving KALETRA.
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.

NDA 21-226/S-020

Page 32

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 $\geq$ 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 3).
Antiparasitic: atovaquone	↓ Atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
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: sildenafil, tadalafil, vardenafil	↑ Sildenafil ↑ Tadalafil ↑ Vardenafil	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin*	↑ Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
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. 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 (see WARNINGS)
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.

NDA 21-226/S-020
Page 33

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.
---	---------------------	---

* See **CLINICAL PHARMACOLOGY** for Magnitude of Interaction – Table 3 and Table 4.

Other Drugs

Drug interaction studies reveal no clinically significant interaction between KALETRA and desipramine (CYP2D6 probe), pravastatin, stavudine, lamivudine, omeprazole or ranitidine.

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

Zidovudine and Abacavir: KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6-2.2 times (mice) and 0.5 times (rats) the human exposure (based on AUC_{0-24hr} measurement) at the recommended dose of 400/100 mg KALETRA twice-daily. Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver.

NDA 21-226/S-020

Page 34

Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA twice-daily regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at 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 twice-daily).

Pregnancy

Pregnancy Category C

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. 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

NDA 21-226/S-020

Page 35

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.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses 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). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. 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**.

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

NDA 21-226/S-020

Page 36

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 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of KALETRA in pediatric patients in clinical trials is ongoing.

Study 940 is an ongoing 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 naive (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m² or 300 mg lopinavir/75 mg ritonavir per m². Naive patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m² dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD₄ cell count was 838 cells/mm³ and mean baseline plasma HIV-1 RNA was 4.7 log₁₀ copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA < 400 copies/mL was 80% for antiretroviral naive patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD₄ cell count was 404 cells/mm³ for antiretroviral naive and 284 cells/mm³ for antiretroviral experienced patients treated

NDA 21-226/S-020

Page 37

through 48 weeks. At 48 weeks, two patients (2%) had prematurely discontinued the study. One antiretroviral naive 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/m² twice-daily regimen without nevirapine and the 300/75 mg/m² 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). KALETRA once-daily has not been evaluated in pediatric patients.

ADVERSE REACTIONS

Adults

Treatment-Emergent Adverse Events

KALETRA has been studied in 891 patients as combination therapy in Phase I/II and Phase III clinical trials. The most common adverse event associated with KALETRA therapy was diarrhea, which was generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to adverse events were 5.8% in KALETRA-treated and 4.9% in nelfinavir-treated patients in Study 863. The incidence of diarrhea was greater for KALETRA once-daily compared to KALETRA twice-daily in Study 418 (see **Table 12** and **INDICATIONS AND USAGE**).

Treatment-Emergent clinical adverse events of moderate or severe intensity in $\geq 2\%$ of patients treated with combination therapy for up to 48 weeks (Phase III) and for up to 360 weeks (Phase I/II) are presented in Table 12. For other information regarding observed or potentially serious adverse events, please see **WARNINGS** and **PRECAUTIONS**.

NDA 21-226/S-020
Page 38

Table 12. Percentage of Patients with Selected Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

	Study 863 (48 Weeks) KALETRA 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	Study 418 (48 Weeks) KALETRA 800/200 mg QD + TDF + FTC (N=115)	KALETRA 400/100 mg BID + TDF + FTC (N=75)	Study 720 (360 Weeks) KALETRA BID² + d4T + 3TC (N=100)
Body as a Whole					
Abdominal Pain	4%	3%	3%	3%	11%
Asthenia	4%	3%	0%	0%	9%
Headache	2%	2%	3%	3%	6%
Cardiovascular System					
Vein distended	0%	0%	0%	0%	3%
Digestive System					
Anorexia	1%	<1%	<1%	1%	2%
Diarrhea	16%	17%	16%	5%	28%
Dyspepsia	2%	<1%	0%	1%	6%
Flatulence	2%	1%	2%	1%	4%
Nausea	7%	5%	9%	8%	16%
Vomiting	2%	2%	3%	4%	6%
Metabolic and Nutritional					
Weight Loss	1%	<1%	0%	0%	2%
Musculoskeletal					
Myalgia	1%	1%	0%	0%	2%
Nervous System					
Depression	1%	2%	1%	0%	0%
Insomnia	2%	1%	0%	0%	3%
Libido decreased	<1%	<1%	0%	1%	2%
Paresthesia	1%	1%	0%	0%	2%
Respiratory					
Bronchitis	0%	0%	0%	0%	2%
Skin and Appendages					
Rash	1%	2%	1%	0%	5%
Urogenital					
Hypogonadism male	0%	0%	0%	0%	2%

1 Includes adverse events of possible, probable, or unknown relationship to study drug.

2 Includes adverse event data from dose group I (200/100 mg BID [N=16] and 400/100 mg BID [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

NDA 21-226/S-020
Page 39

Table 13. Percentage of Patients with Selected Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

	Study 888 (48 Weeks)		Study 957 ² and Study 765 ³ (84-144 Weeks)
	KALETRA 400/100 mg BID + NVP + NRTIs (N=148)	Investigator-selected protease inhibitor(s) + NVP + NRTIs (N=140)	KALETRA BID + NNRTI + NRTIs (N=127)
Body as a Whole			
Abdominal Pain	2%	2%	4%
Asthenia	3%	6%	9%
Chills	2%	0%	0%
Fever	2%	1%	2%
Headache	2%	3%	2%
Cardiovascular			
Hypertension	0%	0%	2%
Digestive System			
Anorexia	1%	3%	0%
Diarrhea	7%	9%	23%
Dyspepsia	1%	1%	2%
Dysphagia	2%	1%	0%
Flatulence	1%	2%	2%
Nausea	7%	16%	5%
Vomiting	4%	12%	2%
Metabolic and Nutritional			
Weight loss	0%	1%	3%
Musculoskeletal			
Myalgia	1%	1%	2%
Nervous System			
Depression	1%	2%	2%
Insomnia	0%	2%	2%
Paresthesia	1%	0%	2%
Skin and Appendages			
Rash	2%	1%	2%

1 Includes adverse events of possible, probable, or unknown relationship to study drug.

2 Includes adverse event data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 84 weeks. Patients receiving KALETRA in combination with NRTIs and efavirenz.

3 Includes adverse event 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.

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

NDA 21-226/S-020

Page 40

Body as a Whole

Allergic reaction, back pain, chest pain, chest pain substernal, cyst, drug interaction, drug level increased, face edema, flu syndrome, hypertrophy, infection bacterial, malaise, neoplasm, and viral infection.

Cardiovascular System

Atrial fibrillation, cerebral infarct, deep thrombophlebitis, deep vein thrombosis, migraine, myocardial infarct, palpitation, postural hypotension, thrombophlebitis, varicose vein, and vasculitis.

Digestive System

Cholangitis, cholecystitis, constipation, dry mouth, enteritis, enterocolitis, eructation, esophagitis, fecal incontinence, gastritis, gastroenteritis, hemorrhagic colitis, hepatitis, hepatomegaly, increased appetite, jaundice, liver fatty deposit, liver tenderness, mouth ulceration, pancreatitis, periodontitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System

Cushing's syndrome, diabetes mellitus, and hypothyroidism.

Hemic and Lymphatic System

Anemia, leukopenia, and lymphadenopathy.

Metabolic and Nutritional Disorders

Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema, and weight gain.

Musculoskeletal System

Arthralgia, arthrosis, bone necrosis, joint disorder, and myasthenia.

Nervous System

NDA 21-226/S-020

Page 41

Abnormal dreams, agitation, amnesia, anxiety, apathy, ataxia, confusion, convulsion, dizziness, dyskinesia, emotional lability, encephalopathy, extrapyramidal syndrome, facial paralysis, hypertonia, nervousness, neuropathy, peripheral neuritis, somnolence, thinking abnormal, tremor, and vertigo.

Respiratory System

Asthma, cough increased, dyspnea, lung edema, pharyngitis, rhinitis, and sinusitis.

Skin and Appendages

Acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritis, seborrhea, skin benign neoplasm, skin discoloration, skin striae, skin ulcer, and sweating.

Special Senses

Abnormal vision, eye disorder, otitis media, taste loss, taste perversion, and tinnitus.

Urogenital System

Abnormal ejaculation, amenorrhea, breast enlargement, gynecomastia, impotence, kidney calculus, nephritis, and urine abnormality.

Post-marketing Experience

The following adverse reactions have been reported during post-marketing use of KALETRA. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to KALETRA exposure.

Body as a Whole

Redistribution/accumulation of body fat has been reported (see **PRECAUTIONS – Fat Redistribution**).

NDA 21-226/S-020

Page 42

Cardiovascular

Bradyarrhythmias.

Skin and Appendages

Stevens Johnson Syndrome and erythema multiforme.

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in Table 14 and Table 15.

Table 14. Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Antiretroviral-Naïve Patients

Variable	Limit ¹	Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)
		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)
Chemistry	High					
Glucose	>250 mg/dL	2%	2%	3%	1%	4%
Uric Acid	>12 mg/dL	2%	2%	0%	3%	5%
SGOT/AST	>180 U/L	2%	4%	5%	3%	10%
SGPT/ALT	>215 U/L	4%	4%	4%	3%	11%
GGT	>300 U/L	N/A	N/A	N/A	N/A	10%
Total Cholesterol	>300 mg/dL	9%	5%	3%	3%	27%
Triglycerides	>750 mg/dL	9%	1%	5%	4%	29%
Amylase	>2 x ULN	3%	2%	7%	5%	4%
Hematology	Low					
Neutrophils	0.75 x 10 ⁹ /L	1%	3%	5%	1%	5%

1 ULN = upper limit of the normal range; N/A = Not Applicable.

Table 15. Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ of Adult Protease Inhibitor-Experienced Patients

	Study 888 (48 Weeks)	Study 957 ² and Study 765 ³ (84-144 Weeks)
--	----------------------	--

NDA 21-226/S-020
Page 43

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)
Chemistry	High			
Glucose	>250 mg/dL	1%	2%	5%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%
SGOT/AST	>180 U/L	5%	11%	8%
SGPT/ALT	>215 U/L	6%	13%	10%
GGT	>300 U/L	N/A	N/A	29%
Total Cholesterol	>300 mg/dL	20%	21%	39%
Triglycerides	>750 mg/dL	25%	21%	36%
Amylase	>2 x ULN	4%	8%	8%
Chemistry	Low			
Inorganic Phosphorus	<1.5 mg/dL	1%	0%	2%
Hematology	Low			
Neutrophils	0.75 x 10 ⁹ /L	1%	2%	4%

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.

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.

Taste aversion, 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 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

NDA 21-226/S-020

Page 44

drug-related clinical adverse event of moderate to severe intensity
observed in $\geq 2\%$ 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 16.

Table 16. Grade 3-4 Laboratory Abnormalities Reported in $\geq 2\%$ Pediatric Patients

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

1 ULN = upper limit of the normal range.

2 Subjects with Grade 3-4 amylase confirmed by elevations in pancreatic amylase.

OVERDOSAGE

KALETRA oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

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

NDA 21-226/S-020

Page 45

protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

DOSAGE AND ADMINISTRATION

KALETRA capsules and oral solution must be taken with food.

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

Adults

Therapy-Naïve Patients

- KALETRA 400/100 mg (3 capsules or 5.0 mL) twice-daily taken with food.
- KALETRA 800/200 mg (6 capsules or 10 mL) once-daily taken with food.

Therapy-experienced Patients

- KALETRA 400/100 mg (3 capsules or 5.0 mL) twice-daily taken with food.

Once-daily administration of KALETRA is not recommended in therapy-experienced patients.

Concomitant therapy: Efavirenz, nevirapine, amprenavir or nelfinavir

A dose increase of KALETRA to 533/133 mg (4 capsules or 6.5 mL) twice-daily taken with food is recommended when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir (see **CLINICAL PHARMACOLOGY– Drug-drug Interactions** and/or **PRECAUTIONS – Table 11**).

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

Pediatric Patients

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/m²) twice-daily taken with food, up to a maximum dose of 400/100 mg in

NDA 21-226/S-020

Page 46

children > 40 kg (5.0 mL or 3 capsules) twice-daily. KALETRA once-daily has not been evaluated in pediatric patients. **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 capsules.** However, as an alternative, the following table contains dosing guidelines for KALETRA oral solution based on body weight. When possible, dose should be administered using a calibrated dosing syringe.

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
<u>Without nevirapine, efavirenz or amprenavir</u>		
7 to < 15 kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
> 10 to < 15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
> 20 to 25 kg		2.75 mL
> 25 to 30 kg		3.5 mL
> 30 to 35 kg		4.0 mL
> 35 to 40 kg		4.75 mL
> 40 kg	Adult dose	5 mL (or 3 capsules)

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

Note: Use adult dosage recommendation for children > 12 years of age.

Concomitant Therapy: Efavirenz, nevirapine or amprenavir

A dose increase of KALETRA oral solution 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/m²) twice-daily taken with food, up to a maximum dose of 533/133 mg in children > 45 kg twice-daily is recommended when used in combination with efavirenz, nevirapine or amprenavir in children 6 months to 12 years of age. The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz, nevirapine or amprenavir in children (see **CLINICAL PHARMACOLOGY– Drug-drug Interactions** and/or **PRECAUTIONS – Table 11**).

NDA 21-226/S-020
Page 47

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
<u>With nevirapine, efavirenz or amprenavir</u>		
7 to < 15 kg	13 mg/kg BID	
7 to 10 kg		1.5 mL
> 10 to < 15 kg		2.0 mL
15 to 45 kg	11 mg/kg BID	
15 to 20 kg		2.5 mL
> 20 to 25 kg		3.25 mL
> 25 to 30 kg		4.0 mL
> 30 to 35 kg		4.5 mL
> 35 to 40 kg		5.0 mL (or 3 capsules)
> 40 to 45 kg		5.75 mL
> 45 kg	Adult dose	6.5 mL (or 4 capsules)

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

Note: Use adult dosage recommendation for children > 12 years of age.

HOW SUPPLIED

KALETRA (lopinavir/ritonavir) capsules are orange soft gelatin capsules imprinted with the corporate **Abbott “ A”** logo and the Abbo-Code PK. KALETRA is available as 133.3 mg lopinavir/33.3 mg ritonavir capsules in the following package sizes:

Bottles of 180 capsules each..... (NDC 0074-3959-77)

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

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,

NDA 21-226/S-020
Page 48

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.

Abbott Laboratories

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

Revised July 2007

------(Perforation)-----

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

ALERT: Find out about medicines that should NOT be taken with KALETRA. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH KALETRA."

Patient Information

KALETRA (kuh-LEE-tra)

Generic Name: lopinavir/ritonavir (lop-IN-uh-veer/rit-ON-uh-veer)

Read this leaflet carefully before you start taking KALETRA. Also, read it each time you get your KALETRA prescription refilled, in case something has changed. This information does not take the place of talking with your doctor when you start this medicine and at check ups. Ask your doctor if you have any questions about KALETRA.

Before taking your medicine, make sure you have received the correct medicine. Compare the name above with the name on your bottle and the appearance of your medicine with the description provided below. Contact your pharmacist immediately if you believe a dispensing error has occurred.

What is KALETRA and how does it work?

KALETRA is a combination of two medicines. They are lopinavir and ritonavir. KALETRA is a type of medicine called an HIV (human

NDA 21-226/S-020

Page 49

immunodeficiency virus) protease (PRO-tee-ase) inhibitor. KALETRA is always used in combination with other anti-HIV medicines to treat people with human immunodeficiency virus (HIV) infection. KALETRA is for adults and for children age 6 months and older.

HIV infection destroys CD₄ (T) cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

KALETRA blocks HIV protease, a chemical which is needed for HIV to multiply. KALETRA reduces the amount of HIV in your blood and increases the number of T cells. Reducing the amount of HIV in the blood reduces the chance of death or infections that happen when your immune system is weak (opportunistic infections).

Does KALETRA cure HIV or AIDS?

KALETRA does not cure HIV infection or AIDS. The long-term effects of KALETRA are not known at this time. People taking KALETRA may still get opportunistic infections or other conditions that happen with HIV infection. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium complex* (MAC) infections.

Does KALETRA reduce the risk of passing HIV to others?

KALETRA does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

How should I take KALETRA?

- You should stay under a doctor's care when taking KALETRA. Do not change your treatment or stop treatment without first talking with your doctor.
- You must take KALETRA every day exactly as your doctor prescribed it. The dose of KALETRA may be different for you than for other patients. Follow the directions from your doctor, exactly as written on the label.
- Dosing in adults (including children 12 years of age and older):
The usual dose for adults is 3 capsules (400/100 mg) or 5.0 mL of the oral

NDA 21-226/S-020

Page 50

solution twice a day (morning and night), in combination with other anti-HIV medicines.

The doctor may prescribe KALETRA as 6 capsules or 10.0 mL of oral solution (800/200 mg) once-daily in combination with other anti-HIV medicines for some patients who have not taken anti-HIV medications in the past.

- Dosing in children from 6 months to 12 years of age:
Children from 6 months to 12 years of age can also take KALETRA. The child's doctor will decide the right dose based on the child's weight.
- Take KALETRA with food to help it work better.
- Do not change your dose or stop taking KALETRA without first talking with your doctor.
- When your KALETRA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to KALETRA and become harder to treat.
- Be sure to set up a schedule and follow it carefully.
- Only take medicine that has been prescribed specifically for you. Do not give KALETRA to others or take medicine prescribed for someone else.

What should I do if I miss a dose of KALETRA?

It is important that you do not miss any doses. If you miss a dose of KALETRA, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

What happens if I take too much KALETRA?

If you suspect that you took more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately.

As with all prescription medicines, KALETRA should be kept out of the reach of young children. KALETRA liquid contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of KALETRA, it could make him/her sick from too

NDA 21-226/S-020

Page 51

much alcohol. Contact your local poison control center or emergency room immediately if this happens.

Who should not take KALETRA?

Together with your doctor, you need to decide whether KALETRA is right for you.

- Do not take KALETRA if you are taking certain medicines. These could cause serious side effects that could cause death. Before you take KALETRA, you must tell your doctor about all the medicines you are taking or are planning to take. These include other prescription and non-prescription medicines and herbal supplements.

For more information about medicines you should not take with KALETRA, please read the section titled "MEDICINES YOU SHOULD NOT TAKE WITH KALETRA."

- Do not take KALETRA if you have an allergy to KALETRA or any of its ingredients, including ritonavir or lopinavir.

Can I take KALETRA with other medications?*

KALETRA may interact with other medicines, including those you take without a prescription. You must tell your doctor about all the medicines you are taking or planning to take before you take KALETRA.

KALETRA can be taken with acid reducing agents (such as omeprazole and ranitidine) with no dose adjustment.

MEDICINES YOU SHOULD NOT TAKE WITH KALETRA:

- Do not take the following medicines with KALETRA because they can cause serious problems or death if taken with KALETRA.
 - Dihydroergotamine, ergonovine, ergotamine and methylergonovine such as Cafergot®, Migranal® D.H.E. 45®, Ergotrate Maleate, Methergine, and others
 - Halcion® (triazolam)
 - Hismanal® (astemizole)
 - Orap® (pimozide)
 - Propulsid® (cisapride)
 - Seldane® (terfenadine)
 - Versed® (midazolam)

NDA 21-226/S-020

Page 52

- Do not take KALETRA with rifampin, also known as Rimactane[®], Rifadin[®], Rifater[®], or Rifamate[®]. Rifampin may lower the amount of KALETRA in your blood and make it less effective.
- Do not take KALETRA with St. John's wort (*hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease KALETRA levels and lead to increased viral load and possible resistance to KALETRA or cross-resistance to other anti-HIV medicines.
- Do not take KALETRA with the cholesterol-lowering medicines Mevacor[®] (lovastatin) or Zocor[®] (simvastatin) because of possible serious reactions. There is also an increased risk of drug interactions between KALETRA and Lipitor[®] (atorvastatin); talk to your doctor before you take any of these cholesterol-reducing medicines with KALETRA.

Medicines that require dosage adjustments:

It is possible that your doctor may need to increase or decrease the dose of other medicines when you are also taking KALETRA. Remember to tell your doctor all medicines you are taking or plan to take.

Before you take Viagra[®] (sildenafil), Cialis[®] (tadalafil), or Levitra[®] (vardenafil) with KALETRA, talk to your doctor about problems these two medicines can cause when taken together. You may get increased side effects of VIAGRA, CIALIS, or LEVITRA such as low blood pressure, vision changes, and penis erection lasting more than 4 hours. If an erection lasts longer than 4 hours, get medical help right away to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

- If you are taking oral contraceptives ("the pill") or the contraceptive patch to prevent pregnancy, you should use an additional or different type of contraception since KALETRA may reduce the effectiveness of oral or patch contraceptives.
- Efavirenz (Sustiva[™]), nevirapine (Viramune[®]), Agenerase (amprenavir) and Viracept (nelfinavir) may lower the amount of KALETRA in your blood. Your doctor may increase your dose of KALETRA if you are also taking efavirenz, nevirapine, amprenavir or nelfinavir. KALETRA should not be taken once-daily with these medicines.
- If you are taking Mycobutin[®] (rifabutin), your doctor will lower the dose of Mycobutin.
- **A change in therapy should be considered if you are taking KALETRA with:**

NDA 21-226/S-020

Page 53

- Phenobarbital
- Phenytoin (Dilantin® and others)
- Carbamazepine (Tegretol® and others)

These medicines may lower the amount of KALETRA in your blood and make it less effective. KALETRA should not be taken once-daily with these medicines.

- If you are taking or before you begin using inhaled Flonase® (fluticasone propionate) talk to your doctor about problems these two medicines may cause when taken together. Your doctor may choose not to keep you on inhaled Flonase®.
- **Other Special Considerations:**
KALETRA oral solution contains alcohol. Talk with your doctor if you are taking or planning to take metronidazole or disulfiram. Severe nausea and vomiting can occur.
- **If you are taking both didanosine (Videx®) and KALETRA:**
Didanosine (Videx®) should be taken one hour before or two hours after KALETRA.

What are the possible side effects of KALETRA?

- This list of side effects is **not** complete. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.
- The most commonly reported side effects of moderate severity that are thought to be drug related are: abdominal pain, abnormal stools (bowel movements), diarrhea, feeling weak/tired, headache, and nausea. Children taking KALETRA may sometimes get a skin rash.
- Blood tests in patients taking KALETRA may show possible liver problems. People with liver disease such as Hepatitis B and Hepatitis C who take KALETRA may have worsening liver disease. Liver problems including death have occurred in patients taking KALETRA. In studies, it is unclear if KALETRA caused these liver problems because some patients had other illnesses or were taking other medicines.
- Some patients taking KALETRA can develop serious problems with their pancreas (pancreatitis), which may cause death. You have a higher chance of having pancreatitis if you have had it before. Tell your doctor if you have nausea, vomiting, or abdominal pain. These may be signs of pancreatitis.
- Some patients have large increases in triglycerides and cholesterol. The long-term chance of getting complications such as heart attacks or stroke due to increases in triglycerides and cholesterol caused by protease inhibitors is not known at this time.

NDA 21-226/S-020

Page 54

- Diabetes and high blood sugar (hyperglycemia) occur in patients taking protease inhibitors such as KALETRA. Some patients had diabetes before starting protease inhibitors, others did not. Some patients need changes in their diabetes medicine. Others needed new diabetes medicine.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.
- Some patients with hemophilia have increased bleeding with protease inhibitors.
- There have been other side effects in patients taking KALETRA. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.

What should I tell my doctor before taking KALETRA?

- *If you are pregnant or planning to become pregnant:* The effects of KALETRA on pregnant women or their unborn babies are not known.
- *If you are breast-feeding:* Do not breast-feed if you are taking KALETRA. You should not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. You should be aware that if your baby does not already have HIV, there is a chance that HIV can be transmitted through breast-feeding.
- *If you have liver problems:* If you have liver problems or are infected with Hepatitis B or Hepatitis C, you should tell your doctor before taking KALETRA.
- *If you have diabetes:* Some people taking protease inhibitors develop new or more serious diabetes or high blood sugar. Tell your doctor if you have diabetes or an increase in thirst or frequent urination.
- *If you have hemophilia:* Patients taking KALETRA may have increased bleeding.

How do I store KALETRA?

- Keep KALETRA and all other medicines out of the reach of children.
- Refrigerated KALETRA capsules and oral solution remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), KALETRA capsules and oral solution should be used within 2 months.
- Avoid exposure to excessive heat.

Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

NDA 21-226/S-020
Page 55

General advice about prescription medicines:

Talk to your doctor or other health care provider if you have any questions about this medicine or your condition. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have any concerns about this medicine, ask your doctor. Your doctor or pharmacist can give you information about this medicine that was written for health care professionals. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.

* The brands listed are trademarks of their respective owners and are not trademarks of Abbott Laboratories. The makers of these brands are not affiliated with and do not endorse Abbott Laboratories or its products.

Abbott Laboratories

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

Revised December 2006