

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-226 / S-017

21-251 / S-011

Trade Name: Kaletra

Generic Name: (lopinavir / ritonavir)

Sponsor: Abbott Laboratories

Approval Date: March 28, 2005

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APPLICATION NUMBER:

21-226 / S-017

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APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-226/S-017
NDA 21-251/S-011

Abbott Laboratories
ATTN: Mary Ellen Snyder
200 Abbott Park Road
D-491, AP30-1E
Abbott Park IL 60064-6157

Dear Ms Snyder:

Please refer to your supplemental new drug applications dated October 13, 2004, received October 13, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KALETRA (lopinavir/ritonavir) capsules and oral solution.

These supplemental new drug applications provide for changes in labeling incorporating fluticasone and trazodone interaction information under the Drug Interactions subsection of the WARNINGS section and Table 9 under Drug Interactions subsection of the PRECAUTIONS section.

We completed our review of this supplemental new drug application. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling for the package insert submitted February 24, 2005.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Vasavi Reddy, RPh, Regulatory Project Manager, at (301) 827-2413.

Sincerely,

{See appended electronic signature page}

Jeffrey Murray, M.D., M.P.H.
Deputy Director
Division of Antiviral Drug Products
Office Drug Evaluation IV
Food and Drug Administration

Attachment:

FDL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jeffrey Murray
3/28/05 10:04:11 AM

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LABELING

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(NOS. 3956 AND 3959)

NEW

KALETRA®

(lopinavir/ritonavir) capsules

(lopinavir/ritonavir) oral solution

R_x ONLY

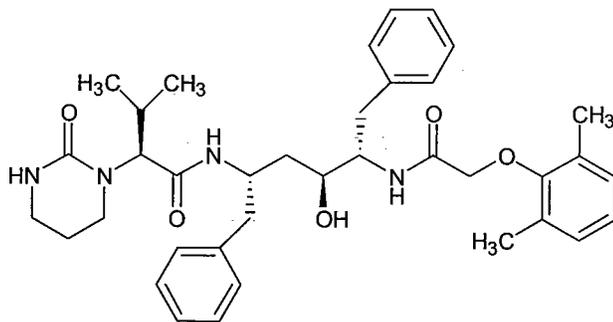
Tear at perforation to dispense patient information.

DESCRIPTION

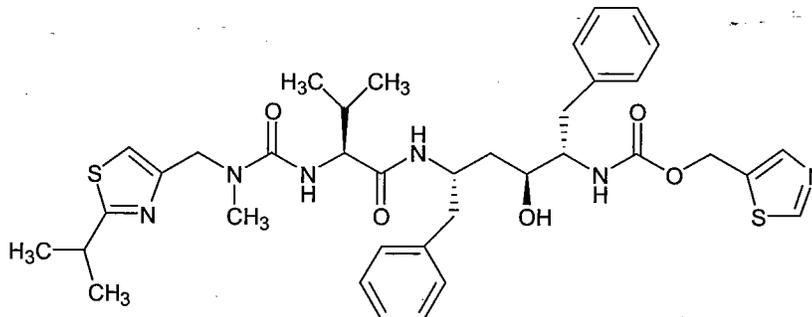
KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

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 C₃₇H₄₈N₄O₅, 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 C₃₇H₄₈N₆O₅S₂, and its molecular weight is 720.95. Ritonavir has the following structural formula:



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

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.

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

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

The selection of resistance to KALETRA in antiretroviral treatment 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%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to KALETRA in antiretroviral treatment naive pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

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

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

Clinical Studies - Antiviral activity of KALETRA in patients with previous protease inhibitor therapies: The clinical relevance of reduced in vitro susceptibility to lopinavir has been examined by assessing the virologic response to KALETRA therapy, with respect to baseline viral genotype and phenotype, in 56 NNRTI-naive patients with HIV RNA >1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir and ritonavir (Study 957). In this study, patients were initially randomized to receive one of two doses of KALETRA in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC50 values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the wild-type EC50. Fifty-five percent (31/56) of these baseline isolates displayed a >4-fold reduced susceptibility to lopinavir. These 31 isolates had a mean reduction in lopinavir susceptibility of 27.9-fold. Table 1 shows the 48 week virologic response (HIV RNA < 400 and < 50 copies) according to susceptibility and number of genotypic mutations at baseline in 50 evaluable patients enrolled in the study (957) described above. Because this was a select patient population and the sample size was small, the data depicted in Table 1 do not constitute definitive clinical susceptibility breakpoints. Additional data are needed to determine clinically significant breakpoints for KALETRA.

Table 1: HIV RNA Response at Week 48 by baseline KALETRA susceptibility and by number of protease inhibitor-associated mutations¹

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%)
Number of protease inhibitor mutations at baseline		
Up to 5	21/23 (91%) ³	19/23 (83%)
>5	17/27 (63%)	14/27 (52%)

¹ Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic

² Fold change in susceptibility from wild type

³ Thirteen of the 23 patient isolates contained PI mutations at positions 82, 84, and/or 90

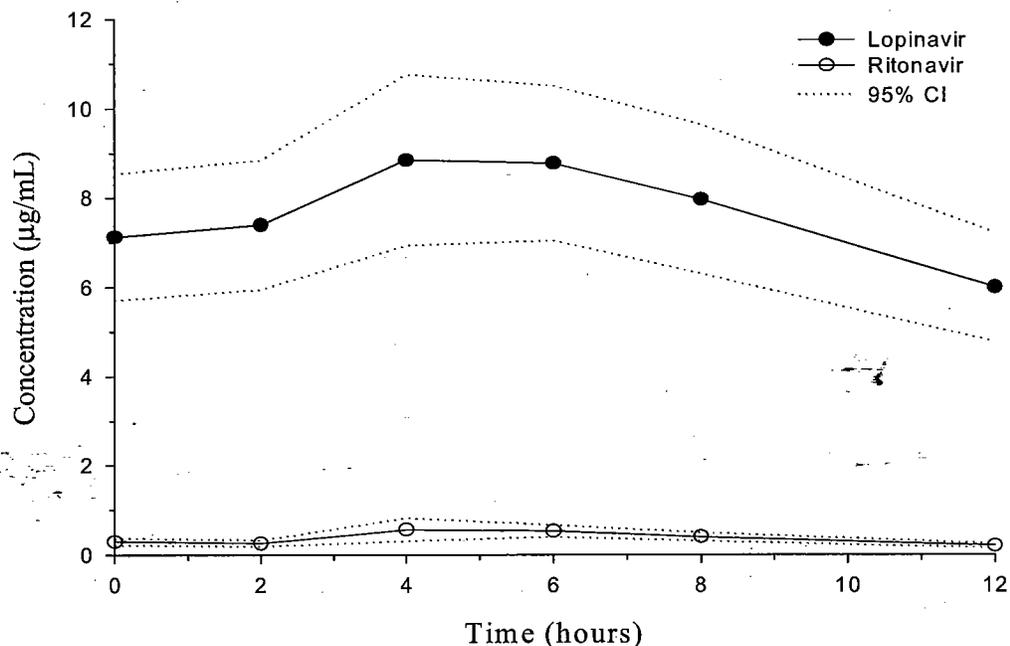
There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

Pharmacokinetics

The pharmacokinetic properties of lopinavir 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 BID 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 BID. 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 BID with food for 3 weeks from a pharmacokinetic study in HIV-infected adult subjects (n=19).

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



Absorption: In a pharmacokinetic study in HIV-positive subjects (n=19), multiple dosing with 400/100 mg KALETRA BID with food for 3 weeks produced a mean \pm SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 µg/mL and minimum concentration within a dosing interval was 5.5 ± 2.7 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 µg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat),

lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA liquid relative to the capsule formulation.

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 BID, 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 ¹⁴C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg KALETRA dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination: Following a 400/100 mg 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)

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.

Pediatric Patients: The pharmacokinetics of KALETRA 300/75 mg/m² BID and 230/57.5 mg/m² BID 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 BID regimen without nevirapine and the 300/75 mg/m² BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

The mean steady-state lopinavir AUC, C_{max}, and C_{min} were 72.6 ± 31.1 µg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 µg/mL, respectively after KALETRA 230/57.5 mg/m² BID 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 BID with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BID (6 months to 8 years) or 4 mg/kg BID (>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. Although KALETRA has not been studied in patients with hepatic impairment, lopinavir concentrations may be increased in these patients (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 2 (effect of other drugs on lopinavir) and Table 3 (effect of KALETRA on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see Table 9 in PRECAUTIONS.

Table 2: Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug

(See PRECAUTIONS, Table 9 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)

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 (>1yr) ²	400/100 BID, steady-state (>1yr)	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID 1 wk ³	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)
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)
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 ⁴	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 ⁵	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
Coadministration of KALETRA and rifampin is not recommended. (See PRECAUTIONS: Table 8 and Table 9)						
Ritonavir ²	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)

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

¹ The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

² Study conducted in HIV-positive adult subjects.

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

⁴ 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.

⁵ 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.

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

Table 3: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA

(See PRECAUTIONS, Table 9 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)
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)	NA
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)
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- <i>O</i> -desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25- <i>O</i> -desacetyl rifabutin ³				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	400/100	10	6.44	9.91	16.54

	combo vs. 1200 TID, 5 d alone	BID, 20 d		(5.59, 7.41)	(8.28, 11.86)	(10.91, 25.08)
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All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.

- ¹ Ratio of parameters for amprenavir, indinavir, nelfinavir, and saquinavir are not normalized for dose.
- ² Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.
- ³ Effect on the dose-normalized sum of rifabutin parent and 25-*O*-desacetyl rifabutin active metabolite.
- * Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.

N/A =not available.

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of KALETRA of 48 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 72 weeks duration.

Description of Clinical Studies

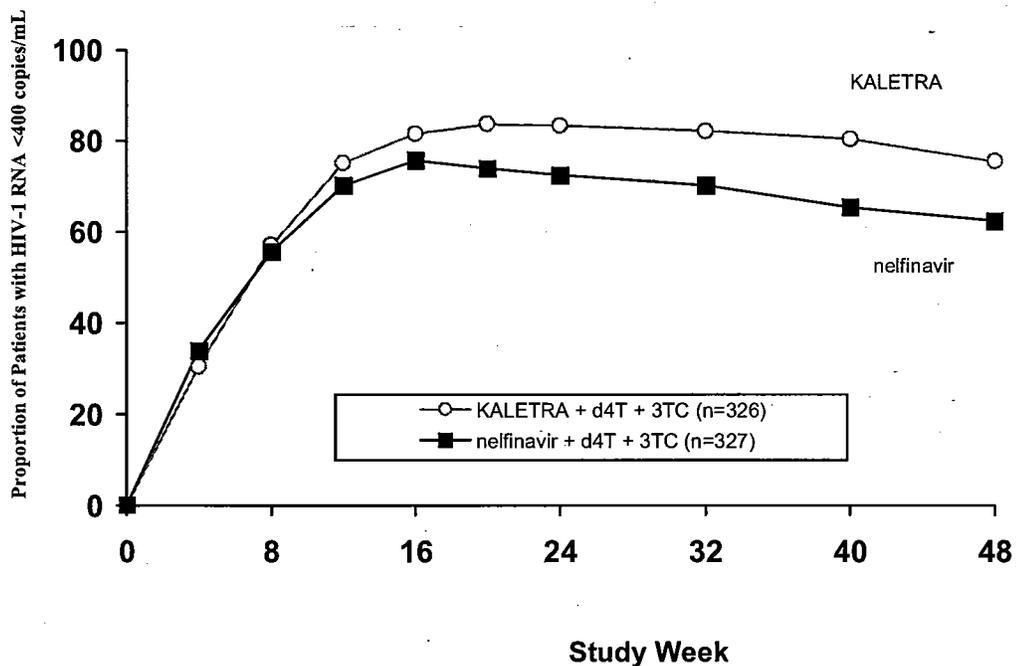
Patients Without Prior Antiretroviral Therapy

Study 863: KALETRA BID + stavudine + lamivudine compared to nelfinavir TID + stavudine + lamivudine

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

Treatment response and outcomes of randomized treatment are presented in Figure 2 and Table 4, respectively.

Figure 2: Virologic Response Through Week 48, Study 863*†



* Roche AMPLICOR HIV-1 MONITOR Assay.

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

Table 4: 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%
Corresponds to rates at Week 48 in Figure 2.		
¹ Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.		
² Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.		
³ Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through week 48, including patients who discontinued subsequent to virologic failure, was 17% in the KALETRA arm and 24% in the nelfinavir arm.		

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV RNA <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 5.

Table 5: Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)

Baseline Viral Load (HIV-1 RNA copies/mL)	KALETRA +d4T+3TC			Nelfinavir +d4T+3TC		
	<400 copies/mL ¹	<50 copies/mL ²	n	<400 copies/mL ¹	<50 copies/mL ²	n
<30,000	74%	71%	82	79%	72%	87
≥30,000 to <100,000	81%	73%	79	67%	54%	79
≥100,000 to <250,000	75%	64%	83	60%	47%	72
≥250,000	72%	60%	82	44%	33%	89

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

² Patients achieved HIV RNA <50 copies/mL at Week 48.

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

Patients with Prior Antiretroviral Therapy

Study 888: KALETRA BID + 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 BID) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naive

NDA 21-226/S-017

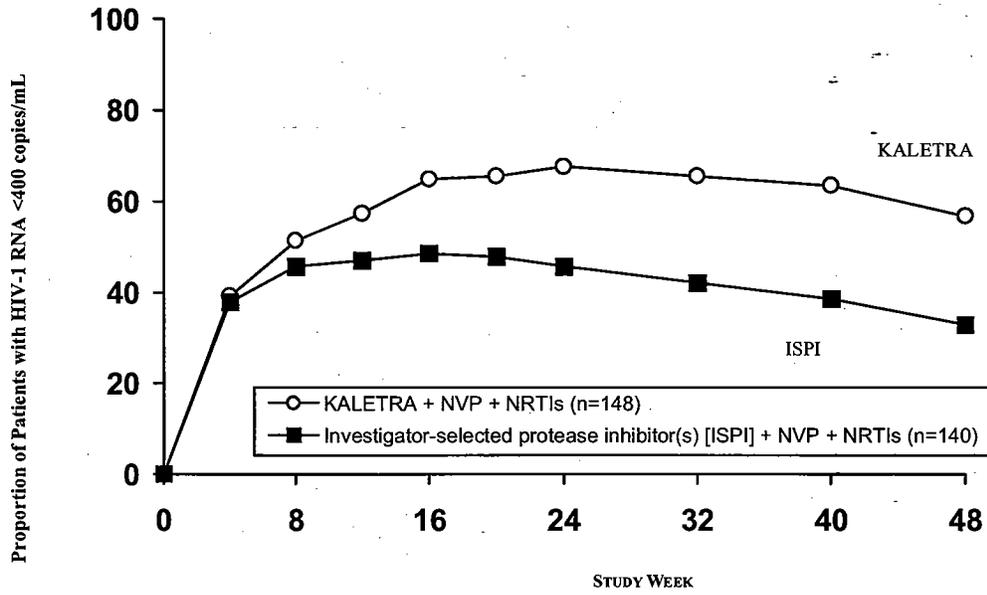
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patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD4 cell count was 322 cells/mm³ (range: 10 to 1059 cells/mm³) and mean baseline plasma HIV-1 RNA was 4.1 log₁₀ copies/mL (range: 2.6 to 6.0 log₁₀ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Figure 3: Virologic Response Through Week 48, Study 888*† and Table 6, respectively.

Figure 3: Virologic Response Through Week 48, Study 888*†



* Roche AMPLICOR HIV-1 MONITOR Assay.

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

Table 6: 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%
* Corresponds to rates at Week 48 in Figure 3.		
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 BID + stavudine + lamivudine

Study 765: KALETRA BID + 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 BID [720 only], 400/100 mg BID, and 400/200 mg BID). 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.

Through 72 weeks of treatment, for patients randomized to the 400/100 mg BID dose of KALETRA, the proportion of patients with plasma HIV-1 RNA <400 (<50) copies/mL was 80% (78%) in study 720 [n=51] and 75% (58%) in study 765 [n=36]. The corresponding mean increase in CD4 cell count was 256 cells/mm³ for study 720 and 174 cells/mm³ for study 765. At 72 weeks, 13 patients (13%) had discontinued study 720 for any reason, including four discontinuations (4%) secondary to adverse events or laboratory abnormalities with one of these discontinuations (1%) being attributed to a KALETRA adverse event. In study 765, 13 patients (19%) had discontinued the study for any reason at 72 weeks, including six discontinuations (9%) secondary to adverse events or laboratory abnormalities with three of these discontinuations (4%) being attributed to KALETRA adverse events.

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 7.

Table 7: 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.

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 7: Drugs That Are Contraindicated With KALETRA, PRECAUTIONS - Table 8: Drugs That Should Not Be Co-administered With KALETRA and Table 9: Established and Other Potentially Significant Drug Interactions).

Particular caution should be used when prescribing sildenafil in patients receiving KALETRA. Co-administration of KALETRA with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see PRECAUTIONS: Drug Interactions and the complete prescribing information for sildenafil.)

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.

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 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. 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).

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 11). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See PRECAUTIONS Table 9: Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

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.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-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 sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see Table 9: 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 and reduce its therapeutic effect (see Table 9: 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 8: 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 8: 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 9 for further details).
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylegonovine	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 (hypericum perforatum)	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 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 9: 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, Tables 2 and 3)**

Concomitant Drug Class: Drug Name	Effect on Concentration of lopinavir or Concomitant Drug	Clinical Comment
<i>HIV-Antiviral Agents</i>		
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). 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.
Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		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).
HIV-Protease Inhibitors: 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 750mg BID, when coadministered. (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY: Table 2 and Table 3). Appropriate doses of the combination of fosamprenavir and KALETRA 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 coadministered with KALETRA 400/100 mg BID (see CLINICAL PHARMACOLOGY: Table 3).
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	Increase KALETRA dose to 533/133 mg and decrease nelfinavir dose to 1000 mg BID, when coadministered. (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY: Table 2 and Table 3).

	nelfinavir ↓ Lopinavir	
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 coadministered with KALETRA 400/100 mg BID.
HIV-Protease Inhibitor: ritonavir*	↑ Lopinavir	Appropriate doses of additional ritonavir in-combination with KALETRA with respect to safety and efficacy have not been established.
<i>Other Agents</i>		
Antiarrhythmics: amiodarone, bepridil, 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.
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 coadministration 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: <ul style="list-style-type: none"> • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole	↑ Ketoconazole ↑ Itraconazole	High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antimycobacterial: rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.

Antimycobacterial: Rifampin	↓ Lopinavir	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co administered antiretroviral agents. A study evaluated combination of rifampin 600 mg QD, with KALETRA 800/200 mg BID or KALETRA 400/100mg + 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 2)
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/metro- nidazole		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).
Erectile Dysfunction Agent: sildenafil	↑ Sildenafil	Use with caution at reduced doses of 25 mg every 48 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. 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 WARNINGS :
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.

Oral Contraceptive: ethinyl estradiol*	↓ Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and KALETRA are co-administered.
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* See **CLINICAL PHARMACOLOGY** for Magnitude of Interaction, **Table 2** and **Table 3**

Other Drugs:

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

Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapson, 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

Long-term carcinogenicity studies of KALETRA in animal systems have not been completed.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. 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 BID). 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. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. 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 BID 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 BID).

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 (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in

humans at the recommended therapeutic dose (400/100 mg BID). 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 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 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 BID regimen without nevirapine and the 300/75 mg/m² BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

ADVERSE REACTIONS**Adults:**

Treatment-Emergent Adverse Events: KALETRA has been studied in 701 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.

Drug related 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 72 weeks (Phase I/II) are presented in Table 10. For other information regarding observed or potentially serious adverse events, please see WARNINGS and PRECAUTIONS.

Table 10: Percentage of Patients with Selected Treatment-Emergent¹ Adverse Events of Moderate or Severe Intensity Reported in $\geq 2\%$ of Adult Patients

	Study 863		Study 888		Other Studies	
	Antiretroviral-Naive Patients 48 Weeks		Protease Inhibitor- Experienced Patients 48 Weeks		Study 720 72 Weeks	Study 957 ³ and Study 765 ⁴ 48-72 Weeks
	KALETRA 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALET RA 400/100 mg BID + NVP + NRTIs (N=148)	Investigator -selected protease inhibitor(s) + NVP + NRTIs (N=140)	KALETRA BID ² + d4T + 3TC (N= 84)	KALETRA BID + NNRTI + NRTIs (N= 127)
Body as a Whole						
Abdominal Pain	4%	3%	2%	2%	5%	2%
Asthenia	4%	3%	3%	6%	7%	8%
Chills	0%	<1%	2%	0%	1%	0%
Fever	<1%	<1%	2%	1%	0%	2%
Headache	2%	2%	2%	3%	7%	2%
Digestive System						
Anorexia	1%	<1%	1%	3%	0%	0%
Diarrhea	16%	17%	7%	9%	24%	18%
Dyspepsia	2%	<1%	1%	1%	1%	0%
Dysphagia	0%	0%	2%	1%	1%	0%
Flatulence	2%	1%	1%	2%	1%	2%
Nausea	7%	5%	7%	16%	15%	4%
Vomiting	2%	2%	4%	12%	5%	2%
Nervous System						
Depression	1%	2%	1%	2%	0%	2%
Insomnia	2%	1%	0%	2%	2%	2%
Skin and Appendages						
Rash	1%	2%	2%	1%	4%	2%

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

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

³ Includes adverse event data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 48 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.

⁴ Includes adverse event data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 72 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.

Body as a Whole: Abdomen enlarged, allergic reaction, back pain, chest pain, chest pain substernal, cyst, drug interaction, drug level increased, face edema, flu syndrome, hypertrophy, infection bacterial, malaise, and viral infection.

Cardiovascular System: Atrial fibrillation, deep vein thrombosis, hypertension, migraine, palpitation, thrombophlebitis, varicose vein, and vasculitis.

Digestive System: Cholangitis, cholecystitis, constipation, dry mouth, enteritis, enterocolitis, eructation, esophagitis, fecal incontinence, gastritis, gastroenteritis, hemorrhagic colitis, increased appetite, jaundice, mouth ulceration, pancreatitis, 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, weight gain, and weight loss.

Musculoskeletal System: Arthralgia, arthrosis and myalgia.

Nervous System: Abnormal dreams, agitation, amnesia, anxiety, apathy, ataxia, confusion, convulsion, dizziness, dyskinesia, emotional lability, encephalopathy, facial paralysis, hypertonia, libido decreased, neuropathy, paresthesia, peripheral neuritis, somnolence, thinking abnormal, and tremor.

Respiratory System: Asthma, bronchitis, 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 ulcer, and sweating.

Special Senses: Abnormal vision, eye disorder, otitis media, and taste perversion, and tinnitus.

Urogenital System: Abnormal ejaculation, gynecomastia, hypogonadism male, kidney calculus, 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).

Cardiovascular: Bradyarrhythmias.

Laboratory Abnormalities: The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in Table 11.

TABLE 11: GRADE 3-4 LABORATORY ABNORMALITIES REPORTED IN ≥ 2% OF ADULT PATIENTS

		Study 863		Study 888		Other Studies	
		Antiretroviral-Naive Patients 48 Weeks		Protease Inhibitor- Experienced Patients 48 Weeks		Study 720 72 Weeks	Study 957 ³ and Study 765 ⁴ 48-72 Weeks
Variable	Limit ¹	KALETRA 400/100 mg BID + d4T + 3TC(N=326)	Nelfinavir 750 mg TID+ d4T + 3TC(N=327)	KALETRA 400/100 mg BID + NVP + NRTIs(N=148)	Investigator -selected protease inhibitor(s) + NVP + NRTIs(N=140)	KALETRA BID ² + d4T + 3TC(N= 84)	KALETRA BID+ NNRTI + NRTIs(N=127)
Chemistry	High						
Glucose	>250 mg/dL	2%	2%	1%	2%	2%	5%
Uric Acid	>12 mg/dL	2%	2%	0%	1%	4%	1%
Total Bilirubin	>3.48 mg/dL	<1%	0%	1%	3%	1%	0%
SGOT/AST	>180 U/L	2%	4%	5%	11%	10%	6%
SGPT/ALT	>215 U/L	4%	4%	6%	13%	8%	10%
GGT	>300 U/L	N/A	N/A	N/A	N/A	4%	28%
Total Cholesterol	>300 mg/dL	9%	5%	20%	21%	14%	33%
Triglycerides	>750 mg/dL	9%	1%	25%	21%	11%	32%
Amylase	>2 x ULN	3%	2%	4%	8%	5%	6%
Chemistry	Low						
Inorganic Phosphorus	<1.5 mg/dL	0%	0%	1%	0%	0%	2%
Hematology	Low						
Neutrophils	0.75 x 10 ⁹ /L	1%	3%	1%	2%	2%	4%

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

² Includes clinical laboratory data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=33]).

³ Includes clinical laboratory data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 48 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.

⁴ Includes clinical laboratory data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 72 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 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 12.

Table 12. 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 x 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 protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

DOSAGE AND ADMINISTRATION

Adults

The recommended dosage of KALETRA is 400/100 mg (3 capsules or 5.0 mL) twice daily taken with food.

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 Interactions** and/or **PRECAUTIONS—Table 9**).

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 children >40 kg (5.0 mL or 3 capsules) twice daily. **It is preferred that the prescriber calculate the appropriate milligram dose for each individual child ≤ 12 years old and determine the corresponding volume of solution or number of 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 <15kg	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 Interactions and/or PRECAUTIONS – Table 9).

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 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, 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.

NEW

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KALETRA®

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NDA 21-251/S-011

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

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®, Ergostrate Maleate, Methergine, and others
 - Halcion® (triazolam)
 - Hismanal® (astemizole)
 - Orap® (pimozide)
 - Propulsid® (cisapride)
 - Seldane® (terfenadine)
 - Versed® (midazolam)

- 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) with KALETRA, talk to your doctor about problems these two medicines can cause when taken together. You may get increased side effects of VIAGRA, 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") to prevent pregnancy, you should use an additional or different type of contraception since KALETRA may reduce the effectiveness of oral 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.
- 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:**
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.

- 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.

- 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.

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.

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Revised: NEW

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NEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-017

21-251 / S-011

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

Division of Antiviral Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: 21-226 (S-017)
21-251 (S-011)
20-945 (S-014)
20-659 (S-032)

Name of Drugs: KALETRA (lopinavir/ritonavir) capsules and oral solution
NORVIR (ritonavir) tablet and oral solution

Applicant: Abbott Laboratories

Material Reviewed:

Submission Date(s): October 13, 2004, February 24, 2005

Receipt Date(s): February 24, 2005

Background and Summary

The Sponsor submitted to the Division labeling changes which incorporate fluticasone and trazodone interaction information in a draft proposal of the Package Inserts (PI) and Patient Package Insert (PPI) for KALETRA and NORVIR on February 24, 2005.

Review

KALETRA LABELING CHANGES:

In addition to the minor editorial and formatting changes, there were reportable changes made to the following sections of the PI for KALETRA: Drug Interactions subsection of the WARNINGS section and Table 9 under Drug Interactions subsection of the PRECAUTIONS section. The following sections of the PI for NORVIR were updated: Table 3 under the drug-drug interaction subsection of the CLINICAL PHARMACOLOGY section; CONTRAINDICATIONS; drug interaction subsection of the WARNINGS section; and Table 6 under Drug Interaction subsection of the PRECAUTIONS section.

Details of Major Changes:

WARNINGS:

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

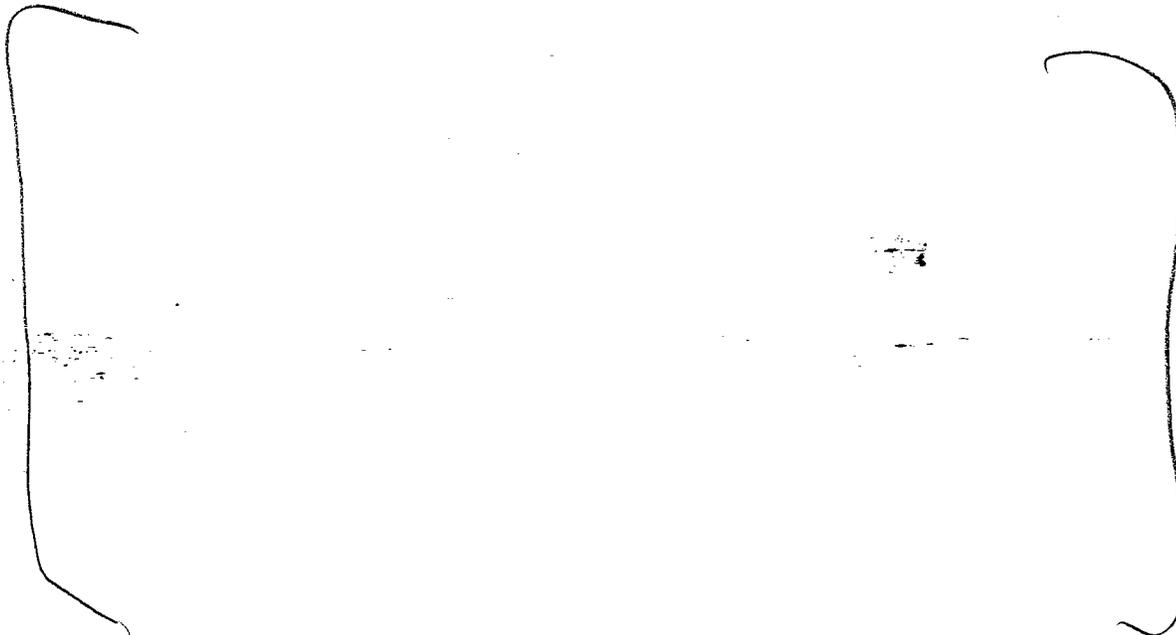
adrenal suppression have been reported during postmarketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Therefore, coadministration of fluticasone propionate and KALETRA is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. (see PRECAUTIONS: Drug Interactions)

PRECAUTIONS:

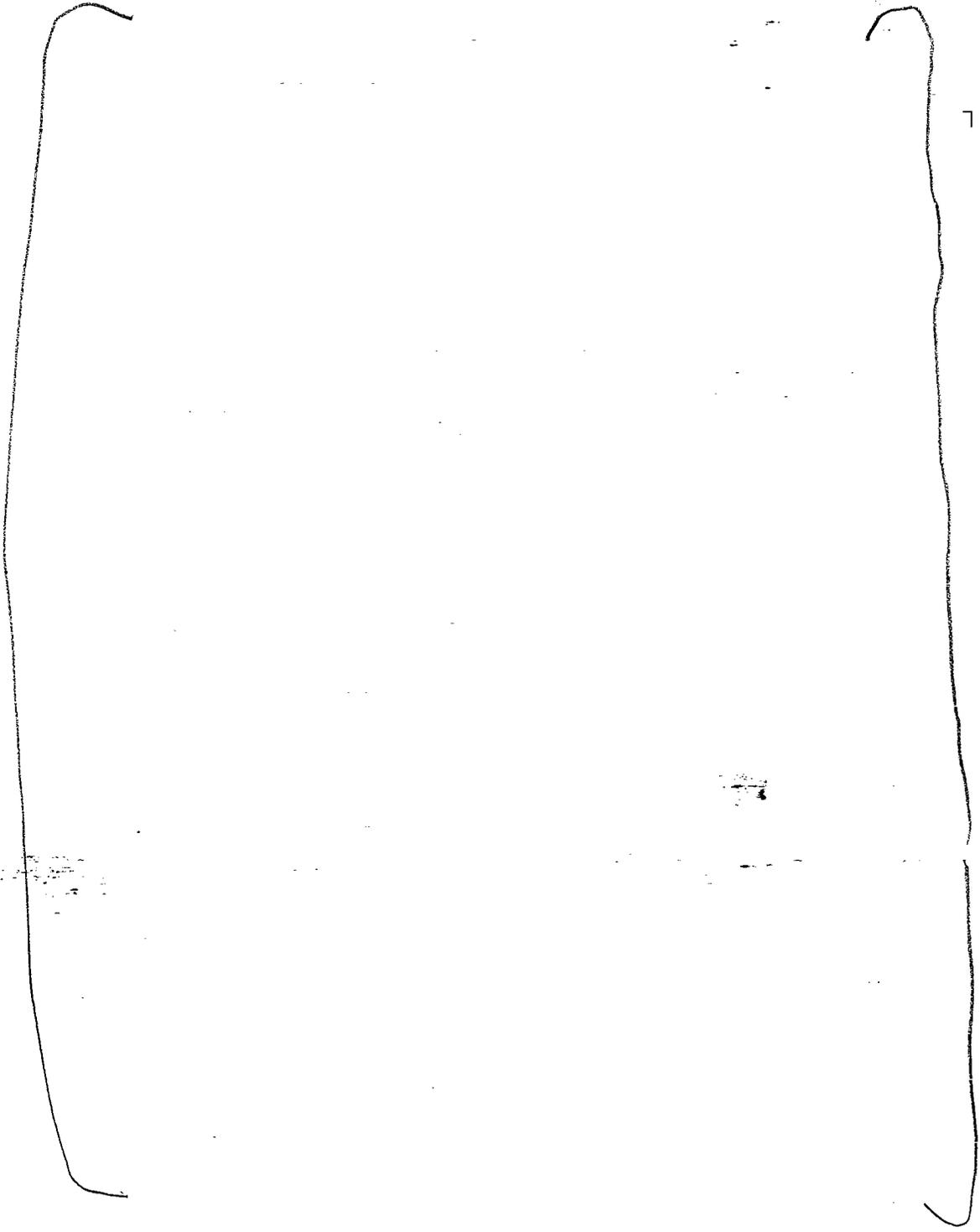
Table 9: Established and Other Potentially Significant Drug Interactions Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction

<p>Inhaled/nasal steroid: Fluticasone</p>	<p>↑ fluticasone</p>	<p>Concomitant use of fluticasone propionate and KALETRA may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. 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 WARNINGS).</p>
<p>Antidepressant: trazodone</p>	<p>↑ trazodone</p>	<p>Concomitant use of trazodone and KALETRA may increase — concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following coadministration 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.</p>

NORVIR LABELING CHANGES:



CONTRAINDICATIONS:



C]

Conclusions:

After reviewing and comparing the last approved label dated October 13, 2004 and the proposed label submitted February 24, 2005, all the reported changes in SLR 017/ 011 are approved.

Vasavi Reddy, RPh., LCDR., USPHS
Regulatory Project Manager, DAVDP

Supervisory Comment/Concurrence:

Anthony DeCicco, RPh., Capt, USPHS
Chief, Project Management Staff, DAVDP

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/s/

David Araojo
3/24/05 02:42:01 PM
CSO

CAPT DeCicco, this is the CSO review for Kaletra and Norvir

Tony DeCicco
3/24/05 02:46:28 PM
CSO