CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-226 / S-014
21-251 / S-010

Trade Name: Kaletra

Generic Name: (lopinavir / ritonavir)

Sponsor: Abbott Laboratories

Approval Date: October 19, 2004

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APPLICATION NUMBER:

21-226 / S-014
21-251 / S-010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-014
21-251 / S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-226/S-014
NDA 21-251/S-010

Mary Ellen Snyder
Global Pharmaceutical Regulatory Affairs
Dept RA76, AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms Snyder:

Please refer to your supplemental new drug applications dated December 19, 2003, received December 19, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KALETRA (Lopinavir/Ritonavir) capsules and oral solution.

This supplemental new drug application provides for the use of KALETRA (Lopinavir/Ritonavir) capsules and oral solution for combination with other antiretroviral agents for the treatment of HIV-infection.

We completed our review of this application as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. The approval was based on review of two phase II trials used to support long-term (Week 144-204) efficacy and safety data.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert, and text for the patient package insert.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-226/S-014." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages neonates to < 6months and adolescents from 12 years to 16 years until December 31, 2006.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Multiple-dose pharmacokinetics, safety and activity study of ABT-378/ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients

   Submission date: December 31, 2006

2. Multiple-dose pharmacokinetic and safety study of ABT-378/ritonavir in HIV-exposed neonates (born to HIV-infected mothers).

   Submission date: December 31, 2006

We also remind you of an additional post-marketing commitment listed below:

3. Please submit resistance datasets according to DAVDP's HIV resistance template from the treatment-experienced studies (M97-765, M98-957, M98-888, and ANRS observation cohort) in order to further characterize the impact of baseline mutations and baseline susceptibility and virologic outcome. Please submit an integrated study report and an NDA labeling supplement to update the Microbiology: Cross Resistance section of the package insert based on results from baseline genotype and phenotype and virologic response analyses from the above referenced treatment-experienced studies.

   Protocol submission: Not applicable
   Study start: Not applicable
   Submission of resistance datasets, integrated study report and labeling supplement: within six months of the date of the letter.

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated **"Required Pediatric Study Commitments"**.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Division Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Food and Drug Administration

Attachment: Label

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
10/19/04 04:48:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-014
21-251 / S-010

LABELING

(Nos. 3956 and 3959)
NEW

KALETRA®

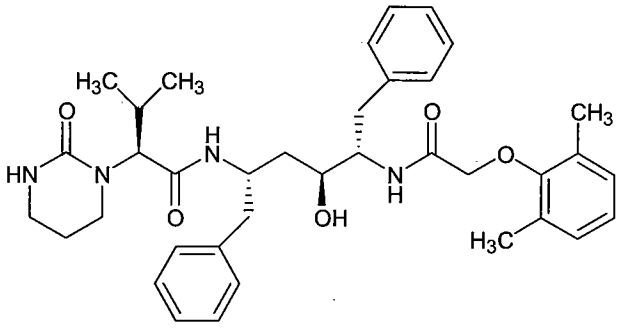
(lopinavir/ritonavir) capsules
(lopinavir/ritonavir) oral solution

R_x only
Tear at perforation to dispense patient information.

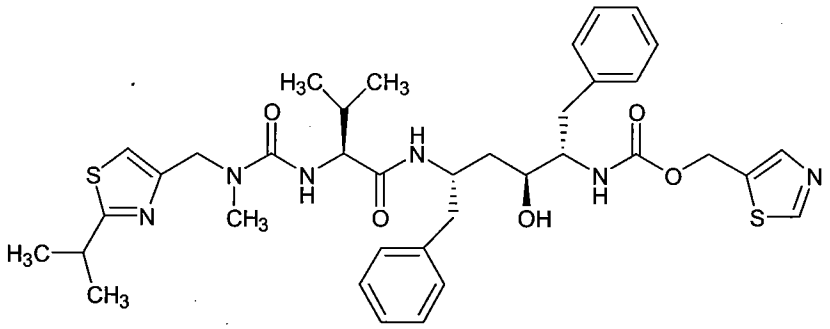
DESCRIPTION

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-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir has the following structural formula:



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



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 (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10-27 nM (0.006 – 0.017 μg/mL, 1 μg/mL = 1.6 μM) and ranged from 4-11 nM (0.003 – 0.007 μg/mL) against several HIV-1 clinical isolates (n=6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 – 289 nM (0.04 – 0.18 μg/mL), representing a 7- to 11-fold attenuation. Combination drug activity studies with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

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

The selection of resistance to KALETRA in antiretroviral treatment 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 EC_{50} values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the wild-type EC_{50}. 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 mutations[1]

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

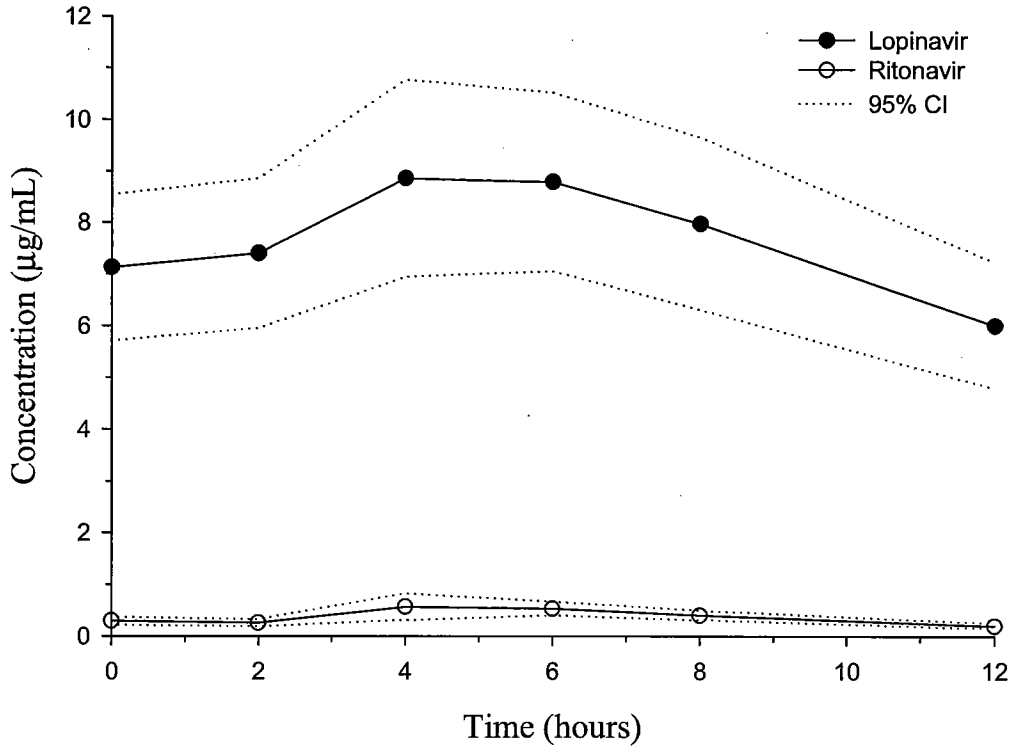
There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

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 EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of KALETRA is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 400/100 mg 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 ± 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 ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg KALETRA dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination: Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 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/m^2 BID and 230/57.5 mg/m^2 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/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 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/m^2 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/m^2 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. Multiple dosing of KALETRA 400/100 mg twice daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment (n=12) resulted in a 30% increase in lopinavir AUC and 20%

increase in C_{max} compared to HIV-infected subjects with normal hepatic function (n=12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31%, respectively). Caution should be exercised when administering KALETRA to subjects with hepatic impairment. KALETRA has not been studied in patients with severe hepatic impairment (see **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)

Fosamprenavir[2]	700 BID plus ritonavir 100 BID, 14 d	400/100 BID, 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 BID, 10 d	400/100 BID, 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 BID, steady-state (>1yr)[3]	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[4]	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[5]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 QD, 14 d	400/400 BID, 9 d[6]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
					Coadministration of KALETRA and rifampin is not recommended. (See **PRECAUTIONS**: Tables 8 and 9)	
Ritonavir[3]	100 BID, 3-4 wk	400/100 BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir[7]	300 mg QD, 14 d	400/100 BID, 14 d	24	NC†	NC†	NC†

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

[1] The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

[2] Data extracted from the fosamprenavir package insert

[3] Study conducted in HIV-positive adult subjects.

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

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

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

[7] Data extracted from the tenofovir package insert.

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

†NC= No Change

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)
Fosamprenavir[3]	700 BID plus ritonavir 100 BID, 14 d	400/100 BID, 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir[1]	600 BID, 10 d combo nonfasting vs. 800 TID, 5 d alone fasting	400/100 BID, 15 d	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nelfinavir[1] M8 metabolite	1000 BID, 10 d combo vs. 1250 BID, 14 d alone	400/100 BID, 21 d	13	0.93 (0.82, 1.05) 2.36 (1.91, 2.91)	1.07 (0.95, 1.19) 3.46 (2.78, 4.31)	1.86 (1.57, 2.22) 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-*0*-desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25-*0*-desacetyl rifabutin[4]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Saquinavir[1]	800 BID, 10 d combo vs. 1200 TID, 5 d alone,	400/100 BID, 15 d	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
	1200 BID, 5 d combo vs. 1200 TID 5 d alone	400/100 BID, 20 d	10	6.44 (5.59, 7.41)	9.91 (8.28, 11.86)	16.54 (10.91, 25.08)
Tenofovir[5]	300 mg QD, 14 d	400/100 BID, 14d	24	NC[†]	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] Ratio of parameters for amprenavir, indinavir, nelfinavir, and saquinavir are not normalized for dose.
[2] Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.
[3] Data extracted from the fosamprenavir package insert
[4] Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.
[5] Data extracted from the tenofovir package insert.
* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.
N/A =not available.
[†] NC= No Change

INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD_4 cell counts in controlled studies of KALETRA of 48 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 144-204 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 CD_4

cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 $\log_{10}$ copies/mL (range: 2.6 to 6.8 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 4.

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
7100,000 to <250,000	75%	64%	83	60%	47%	72
7250,000	72%	60%	82	44%	33%	89

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

Through 48 weeks of therapy, the mean increase from baseline in CD_4 cell count was 207 cells/mm^3 for the KALETRA arm and 195 cells/mm^3 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 patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline CD_4 cell count was 322 cells/mm^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 $\log_{10}$ copies/mL (range: 2.6 to 6.0 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 6.

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 CD_4 cell count was 111 cells/mm^3 for the KALETRA arm and 112 cells/mm^3 for the investigator-selected protease inhibitor(s) arm.

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). In Study 720, all patients switched to 400/100 mg BID between Weeks 48-72. Patients in study 720 had a mean age of 35 years, 70% were Caucasian, and 96% were male, while patients in study 765 had a mean age of 40 years, 73% were Caucasian, and 90% were male. Mean (range) baseline CD_4 cell counts for patients in study 720 and study 765 were 338 (3-918) and 372 (72-807) cells/mm^3, respectively. Mean (range) baseline plasma HIV-1 RNA levels for patients in study 720 and study 765 were 4.9 (3.3 to 6.3) and 4.0 (2.9 to 5.8) $\log_{10}$ copies/mL, respectively.

Through 204 weeks of treatment in study 720, the proportion of patients with HIV RNA <400 (<50) copies/mL was 71% (70%) [n=100], and the corresponding mean increase in CD4 cell count was 440 cells/mm^3. Twenty-eight patients (28%) discontinued the study, including 9 (9%) discontinuations due to adverse events and 1 (1%) death. Through 144 weeks of treatment in study 765, the proportion of patients with HIV RNA <400 (<50) copies/mL was 54% (50%) [n=70], and the corresponding mean increase in CD4 cell count was 212 cells/mm^3. Twenty-seven patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths.

CONTRAINDICATIONS

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

Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 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, tadalafil, or vardenafil in patients receiving KALETRA. Co-administration of KALETRA with these drugs is expected to substantially increase their concentrations and may result in an increase in associated adverse events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS: Drug Interactions** and the complete prescribing information for sildenafil tadalafil, and vardenafil.)

Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs.

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

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 (see **CLINICAL PHARMACOLOGY**, hepatic impairment). Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of KALETRA treatment.

Resistance/Cross-resistance

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

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.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including KALETRA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium*

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

Information for Patients

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

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

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

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

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

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

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

KALETRA should be taken with food to enhance absorption.

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

Drug Interactions

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and PDE5 inhibitors) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **Table 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, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (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 the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Table 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
HIV-Antiviral Agents		
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).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir	↑ tenofovir	KALETRA increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving KALETRA and tenofovir should be monitored for tenofovir-associated adverse events.
HIV-Protease 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:** Tables 2 and 3). Appropriate doses of the combination of fosamprenavir and KALETRA have not been established.
HIV-Protease Inhibitors: fosamprenavir	↓ amprenavir ↓ Lopinavir	An increased rate of adverse events has been observed with coadministration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-Protease Inhibitor: indinavir*	↑ indinavir (indinavir 600 mg BID + KALETRA produces similar AUC, ↓ C_{max}, ↑ C_{min} relative to indinavir 800 mg TID	Decrease indinavir dose to 600 mg BID, when 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 nelfinavir ↓ Lopinavir	Increase KALETRA dose to 533/133 mg and decrease nelfinavir dose to 1000 mg BID, when coadministered.(see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY:** Tables 2 and 3).
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.
		Other Agents
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.
Anti-infective: clarithromycin	↑ Clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole, voriconazole	↑ Ketoconazole ↑ Itraconazole Voriconazole effect is unknown.	High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended. Coadministration of voriconazole with KALETRA has not been studied. However, administration of voriconazole with ritonavir 400 mg every 12 hours decreased voriconazole steady-state AUC by an average of 82%. The effect of lower ritonavir doses on voriconazole is not known at this time. Until data are available, voriconazole should not be administered to patients receiving KALETRA.
Antimycobacterial: rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of

		rifabutin may be necessary.
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 7 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/ metronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ Sildenafil ↑ Tadalafil ↑ Vardenafil	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events. Use vardenafil with caution at reduced doses of no more then 2.5 mg every 72 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin*	↑ Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Immunosuppresants: cyclosporine, tacrolimus, rapamycin	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Narcotic Analgesic: Methadone*	↓ Methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.
Oral Contraceptive: ethinyl estradiol*	↓ Ethinyl estradiol	Because contraceptive steroid concentrations may be altered when KALETRA is coadministered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.

* See **CLINICAL PHARMACOLGY** for Magnitude of Interaction, Tables 2 and 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, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

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

Carcinogenesis, Mutagenesis and Impairment of Fertility
Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6-2.2 times (mice) and 0.5 times (rats) the human exposure (based on $AUC_{0\text{-}24hr}$ measurement) at the recommended dose of 400/100 mg KALETRA twice daily. Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. 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. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA 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. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg 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.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg 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 m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. 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 m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD_4 cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA < 400 copies/mL was 80% for antiretroviral naive patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD_4 cell count was 404 cells/mm^3 for antiretroviral naive and 284 cells/mm^3 for antiretroviral experienced patients treated through 48 weeks. At 48 weeks, two patients (2%) had prematurely discontinued the study. One antiretroviral 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/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 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 ≥ 2% of patients treated with combination therapy for up to 48 weeks (Phase III) and for up to 204 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-Emergent[1] Adverse Events of Moderate or Severe Intensity 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 (204 Weeks)	Study 957[2] and Study 765[3] (84-144 Weeks)
	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 + d4T + 3TC (N= 100)	KALETRA BID + NNRTI + NRTIs (N= 127)
Body as a Whole						
Abdominal Pain	4%	3%	2%	2%	10%	4%
Asthenia	4%	3%	3%	6%	9%	9%
Chills	0%	<1%	2%	0%	0%	0%
Fever	<1%	<1%	2%	1%	0%	2%
Headache	2%	2%	2%	3%	7%	2%
Cardiovascular						
Hypertension	0%	0%	0%	0%	0%	2%
Vein distended	0%	0%	0%	0%	2%	0%
Digestive System						
Anorexia	1%	<1%	1%	3%	2%	0%
Diarrhea	16%	17%	7%	9%	27%	23%
Dyspepsia	2%	<1%	1%	1%	5%	2%
Dysphagia	0%	0%	2%	1%	0%	0%
Flatulence	2%	1%	1%	2%	4%	2%
Nausea	7%	5%	7%	16%	16%	5%
Vomiting	2%	2%	4%	12%	6%	2%
Metabolic and Nutritional						
Weight loss	1%	<1%	0%	1%	2%	3%
Musculoskeletal						
Myalgia	1%	1%	1%	1%	2%	2%
Nervous System						
Depression	1%	2%	1%	2%	0%	2%

Insomnia	2%	1%	0%	2%	2%	2%
Libido decreased	<1%	<1%	1%	0%	2%	0%
Paresthesia	1%	1%	0%	1%	2%	2%
Respiratory						
Bronchitis	0%	0%	0%	0%	2%	0%
Skin and Appendages						
Rash	1%	2%	2%	1%	4%	2%
Urogenital						
Hypogonadism male	0%	0%	0%	0%	2%	0%

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

[2] Includes adverse event data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 84 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.
[3] Includes adverse event data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 144 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.

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

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

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

Digestive System: Cholangitis, cholecystitis, constipation, dry mouth, enteritis, enterocolitis, eructation, esophagitis, fecal incontinence, gastritis, gastroenteritis, hemorrhagic colitis, increased appetite, jaundice, mouth ulceration, pancreatitis, periodontitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System: Cushing's syndrome, diabetes mellitus, and hypothyroidism.

Hemic and Lymphatic System: Anemia, leukopenia, and lymphadenopathy.

Metabolic and Nutritional Disorders: Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema, and weight gain.

Musculoskeletal System: Arthralgia, arthrosis and bone necrosis.

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

Respiratory System: Asthma, 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, taste perversion, and tinnitus.

Urogenital System: Abnormal ejaculation, breast enlargement, gynecomastia, 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.

Skin and Appendages: Stevens Johnson Syndrome and erythema multiforme.

Laboratory Abnormalities: The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in Table 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 (204 Weeks)	Study 957[2] and Study 765[3] (84-144 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 + d4T + 3TC (N= 100)	KALETRA BID + NNRTI + NRTIs (N= 127)
Chemistry	High						
Glucose	>250 mg/dL	2%	2%	1%	2%	4%	5%
Uric Acid	>12 mg/dL	2%	2%	0%	1%	3%	1%
Total Bilirubin	>3.48 mg/dL	<1%	0%	1%	3%	1%	1%
SGOT/AST	>180 U/L	2%	4%	5%	11%	9%	8%
SGPT/ALT	>215 U/L	4%	4%	6%	13%	9%	10%
GGT	>300 U/L	N/A	N/A	N/A	N/A	6%	29%
Total Cholesterol	>300 mg/dL	9%	5%	20%	21%	22%	39%
Triglycerides	>750 mg/dL	9%	1%	25%	21%	22%	36%
Amylase	>2 x ULN	3%	2%	4%	8%	4%	8%
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%	5%	4%

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

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

[3] Includes clinical laboratory data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 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 ≥ 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 ≥ 2% Pediatric Patients

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

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

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/m^2) 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)
Without nevirapine, efavirenz or amprenavir		
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/m^2) 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 or nevirapine 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)
With nevirapine, efavirenz or amprenavir		
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

ABBOTT
LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

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

KALETRA™

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

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

Patient Information

KALETRA™ (kuh-LEE-tra)

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

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

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

What is KALETRA and how does it work?

KALETRA is a combination of two medicines. They are lopinavir and ritonavir. KALETRA is a type of medicine called an HIV (human 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 CD_4 (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®, Ergotrate 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), Cialis® (tadalafil), or Levitra® (vardenafil) with KALETRA, talk to your doctor about problems these medicines can cause when taken together. You may get increased side effects of VIAGRA, CIALIS, or LEVITRA such as low blood pressure, vision changes, and penis erection lasting more than 4 hours. If an erection lasts longer than 4 hours, get medical help right away to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

- If you are taking oral contraceptives ("the pill") or the contraceptive patch to prevent pregnancy, you should use an additional or different type of contraception since KALETRA may reduce the effectiveness of oral or patch contraceptives.

- Efavirenz (Sustiva™), nevirapine (Viramune®), Agenerase (amprenavir) and Viracept (nelfinavir) may lower the amount of KALETRA in your blood. Your doctor may increase your dose of KALETRA if you are also taking efavirenz, nevirapine, amprenavir or nelfinavir.

- 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.

- **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 you 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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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-014
21-251 / S-010

MEDICAL REVIEW

JOINT CLINICAL AND STATISTICAL REVIEW

NDA 21-226/21-251

Date Submitted:		December 19, 2003
Date Completed:		September 13, 2004
Applicant:		Abbott Laboratories 200 Abbott Park Road D-491, AP30-1E Abbott Park, Illinois 60064-6157
Drug:	Generic:	lopinavir/ritonavir
	Trade:	Kaletra®
Drug class:		Antiviral agent – Protease Inhibitor
Route of administration:		Oral
Dosage form:		Co-formulated soft gel capsules (133.3 mg lopinavir/33.3 mg ritonavir) Co-formulated oral solution (80 mg lopinavir/20 mg ritonavir per ml)
Proposed Indication:		Treatment of HIV infection
Related INDs:		51715
Related NDAs:		21-251
Medical Reviewer:		Kimberly A. Struble, PharmD
Statistical Reviewer:		Rafia Bhore, Ph.D.

Table of Contents

Executive Summary Section

I. Recommendations

The executive summary contains the recommendations and the summary of clinical findings for KALETRA (lopinavir/ritonavir; LPV/RTV) for the treatment of HIV-1 Infection (NDA 21-226 SE2 014). The supplemental application includes two phase II trials to support long-term (Week 144 - 204) efficacy and safety data. The 204-week results from study M97-720 are presented in support of long-term safety and efficacy in antiretroviral-naïve subjects. Study M97-765 is updated to include 144-week efficacy and safety results in antiretroviral-experienced subjects. In addition, results of a multiple dose study in HIV and HCV co-infected subjects with mild to moderate hepatic impairment and Week 104 mice and rat data were submitted to update the respective sections of the package insert. Please refer to the Clinical Pharmacology and Pharmacology/Toxicology review for details.

A. Recommendation on Approvability

From a clinical perspective, the data presented in this supplement support the long-term safety and efficacy of LPV/RTV 400/100 mg twice daily in treatment-naïve and treatment-experienced subjects. Through four years of follow-up, antiretroviral-naïve subjects receiving LPV/RTV achieved and maintained durable HIV RNA suppression and significant increases in CD4 cell counts. Similar observations were observed in antiretroviral-experienced subjects. At Week 144, more than 50% of subjects achieved and maintained HIV RNA < 400 copies/mL. Overall, the 400/100 mg and 400/200 mg dose groups were comparable with respect to virologic and immunologic response. A trend was observed towards a higher proportion of subjects with baseline HIV RNA > 10,000 copies/mL in the 400/200 mg group (53%) achieving HIV RNA < 50 copies/mL compared to the 400/100 mg dose group (38%). This difference was not statistically significant. Of note, significant differences in baseline phenotypic susceptibility to LPV/RTV were seen between the two dose groups. Mean fold change in EC_{50} to LPV/RTV relative to wild type virus was 1.7-fold for the 29 viral isolates from subjects in the 400 mg/100 mg dose group and 3.9-fold for the 30 viral isolates from subjects in the 400 mg/200 mg dose group (p=0.083). The results of the trial are based on a small population (n=70) and the study was not powered to detect statistical differences between the dose groups. Abbott has an outstanding phase IV commitment to evaluate the activity of higher doses of LPV/RTV in subjects exhibiting virologic failure or showing reduced susceptibility to multiple PIs. Nevertheless, subjects receiving LPV/RTV 400/100 mg bid in combination with a NNRTI and NRTIs achieved and maintained an adequate virologic response through 144 weeks of treatment.

Review of the safety data submitted in this supplement did not identify any new or unexpected toxicities. The observed toxicities do not outweigh the clear benefit of LPV/RTV as a treatment option for antiretroviral-naïve and experienced subjects.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Submit resistance datasets according to the Division's HIV resistance template from the treatment-experienced studies (M97-765, M98-957 and M98-888) in order to further characterize the impact of baseline mutations and baseline susceptibility and virologic outcome. Submit an NDA labeling supplement to update the Microbiology: Cross Resistance section of the package insert based on results from baseline genotype and phenotype and virologic response analyses from the above referenced treatment-experienced studies.

Protocol submission: Not applicable
Study start: Not applicable
Submission of resistance datasets, analyses and labeling supplement within 6 months of the date of the letter.

Executive Summary Section

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Trade Name: Kaletra
Class: Protease Inhibitor
Formulation: Capsules
Dosage: 400/100 mg bid

Number of important trials: Two studies, M97-720 and M97-765, were submitted in this supplement.

Number of subjects enrolled in these trials: One hundred subjects in study M97-720 were enrolled, of which 51 subjects were randomized to receive the approved dose (400/100 mg bid). The remaining 49 subjects received either 200/100 mg or 400/200 mg for 48-72 weeks followed by 400/100 mg through Week 204. Seventy subjects in study M97-765 were enrolled, of which 36 subjects received 400/100 mg bid. Thirty-four subjects received 400/200 mg bid.

Indications studied: Treatment of HIV infection

Efficacy and safety data from two phase I/II studies evaluating the use of LPV/RTV in combination with other antiretroviral agents for the treatment of HIV infection were included in the supplement. Originally, studies M97-720 and M97-765 served as the basis for the dose selection for phase III trials.

Study M97-720 enrolled 100 HIV-infected, treatment-naïve subjects. One hundred antiretroviral-naïve subjects with HIV RNA $\geq$ 5,000 copies/mL were randomized to receive one of the following LPV/RTV dose regimens in combination with stavudine (d4T) and lamivudine (3TC):

- 200/100 mg bid
- 400/100 mg bid
- 400/200 mg bid

All subjects remaining in the trial at Week 48 were converted to open-label LPV/RTV 400/100 mg between Weeks 48 and 72.

Study M97-765 enrolled 70 subjects currently receiving a PI-based regimen. Subjects were randomized to receive either LPV/RTV 400/100 mg bid or 400/200 mg bid in combination with nevirapine and NRTIs (at least one new NRTI the subject had not previously received).

B. Efficacy

After a thorough review of the data presented in this supplement, the review team concluded LPV/RTV 400/100 mg BID in combination with other antiretroviral agents provided effective treatment in antiretroviral-naïve and antiretroviral experienced subjects through Week 204 and 144, respectively. The determination of efficacy was based on well-accepted endpoints (analyses of HIV RNA levels) and was consistent with analyses conducted for other studies in subjects receiving PI-based antiretroviral regimens.

The studies included in this supplement were phase II dose-finding trials. After the 400/100 mg dose was selected for further development, studies M97-720 and M97-765 were continued to collect long-term safety and efficacy information. In the treatment-naïve study (M97-720) all subjects assigned to other doses at baseline were switched to the 400/100 mg dose between Weeks 48 and 72. In the treatment-experienced study (M97-765) the dose comparison between 400/100 mg and 400/200 mg continued through Week 144. Although the sample sizes for the two

trials are small, these trials provide important evidence in support of long-term administration of LPV/RTV.

In study M97-720, the response rate (HIV RNA< 400 copies/mL) for antiretroviral-naïve subjects was 71% at Week 204. In antiretroviral-experienced subjects (M97-765), response rates were similar for the two dose groups, 400/100 mg and 400/200 mg. Approximately 50% of subjects enrolled in this study achieved HIV RNA < 400 copies/mL at Week 144.

C. Safety

The safety analyses for this supplement include 170 subjects who received LPV/RTV 400/100 mg or 400/200 mg for approximately 3-4 years. In general, subjects receiving LPV/RTV are representative of the HIV population. Subjects were monitored appropriately to identify significant safety risks. Subjects were evaluated for adverse events (AEs) and laboratory abnormalities every four to eight weeks, which is consistent with follow-up in other ARV studies.

In general, the AE profile for LPV/RTV was not significantly different than observed during the original and supplemental NDA reviews. The most commonly reported AEs observed in the two trials were related to GI disorders, including diarrhea/abnormal stools and nausea. Overall, 10% of subjects discontinued study due to an AE or HIV-related event. AEs leading to study discontinuation were consistent with the AE profile of the study medications used in the trials. No new or unexpected safety findings were observed. Although not new, additional cases of serious skin reactions were reported through the Adverse Event Reaction System (AERS), leading to the addition of Stevens Johnson Syndrome and erythema multiforme events to the Adverse Reaction section of the package insert.

The type and incidence of laboratory abnormalities observed were similar to those seen with other ARVs. The most commonly reported grade 3/4 laboratory abnormalities were increases in cholesterol and triglycerides. Subjects with baseline cholesterol > 200 mg/dL and baseline triglycerides > 400 mg/dL were at increased risk for grade 3/4 elevations in triglycerides. This observation was seen in both treatment-naïve and treatment-experienced subjects. No subjects had concurrent triglycerides > 1000 mg/dL and pancreatitis. Increases in transaminases were also observed. Subjects co-infected with hepatitis B or C were at a significantly increased risk for developing grade 3/4 transaminase elevations. These findings are consistent with previous studies with LPV/RTV. In addition, the observed changes in ECG parameters were not clinically significant.

D. Dosing

The currently approved dose of 400/100 mg bid is effective in decreasing HIV RNA and increasing CD4 cell counts in antiretroviral-experienced and antiretroviral-naïve subjects over 144-204 weeks. Changes to the current dosing regimen are not warranted at this time.

E. Special Populations

Adequate labeling exists for children > 6 months of age and adults. Studies in children < 6 months of age are ongoing. This supplement contains dosing information for subjects with mild to moderate hepatic impairment. Please refer to the Clinical Pharmacology review for details.

Multiple doses of LPV/RTV 400/100 mg bid administered to HIV and HCV co-infected subjects with mild to moderate hepatic impairment (n=12) resulted in a 30% increase in LPV AUC and 20% increase in Cmax compared to HIV-infected subjects with normal hepatic function (n=12). No dose adjustments are required for subjects with mild to moderate hepatic impairment. LPV is principally metabolized and eliminated by the liver; therefore, caution should be exercised when

administering LPV/RTV to subjects with hepatic impairment. No data exists regarding dosing in subjects with severe hepatic impairment.

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

LPV is a peptidomimetic HIV-1 protease inhibitor and selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature infectious virions. The mechanism of action of LPV/RTV is similar to other PIs used in the treatment of HIV infection. Currently, LPV/RTV 400/100 mg given orally twice daily is indicated for the treatment of HIV infection in combination with other antiretroviral agents. As stated previously, this supplement provides data for long-term efficacy and safety (Weeks 144-204) in antiretroviral-naïve and antiretroviral-experienced subjects.

B. State of Armamentarium for Indication

At present, 20 antiretroviral drug products are approved in the US for the treatment of HIV infection, some in multiple formulations and fixed drug combinations. Four classes of antiretroviral agents exist. The classes are based on the mechanism of action in the HIV life cycle: NRTIs, NNRTIs, PIs and fusion inhibitors.

Eight NRTI's are approved and marketed in the US: zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), emtricitabine (Emtriva®), and tenofovir (Viread®). The approved NNRTIs include delavirdine (Rescriptor®), nevirapine (Viramune®), and efavirenz (Sustiva®). The PI class is comprised of the following agents: indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®), atazanavir (Reyataz®), lopinavir/ritonavir fixed dose combination (Kaletra®) and fosamprenavir (Lexiva®). Finally, enfuvirtide (Fuzeon®), a GP41 fusion inhibitor, is approved for use in the US.

C. Important Milestones in Product Development

LPV/RTV is a co-formulation of two PIs. LPV is the active antiretroviral agent and RTV serves as a pharmacologic enhancer by inhibiting the metabolism of LPV via the CYP3A system. Both the soft gel capsule and oral solution formulations of Kaletra were granted accelerated approval on September 15, 2000. The basis for accelerated approval were results from one phase III trial in antiretroviral-naïve and an interim phase III report in PI-experienced subjects showing substantial declines in HIV-1 RNA levels and increases in CD4 cell counts over 24 weeks. In addition, results from 3 phase I/II trials through 24-72 weeks were provided. Review of efficacy supplements containing 48-week data from an adult Phase III clinical trial (21-226, SE8-003) and the on-going pediatric study (21-251, SE8-004) were completed in January, 2002, and results were incorporated into the product label. Traditional approval was granted in November 2002, after review of 48 week data from a second phase 3 clinical trial.

D. Other Relevant Information

Kaletra is approved in 74 countries for the treatment of HIV infection.

E. Important Issues with Pharmacologically Related Agents

Class-related AEs/laboratory abnormalities and potentially significant drug-drug interactions are common for the approved PIs. RTV is the hallmark PI for drug-drug interactions due to its potent inhibition of CYP3A metabolism. In Kaletra, LPV is the active antiretroviral agent and RTV serves as a pharmacologic enhancer by inhibiting the metabolism of LPV via the CYP3A system. Because LPV is co-formulated with RTV, the potential exists for numerous drug-drug interactions, some with clinically significance. Various interactions studies between LPV/RTV and other

commonly used medications in HIV-infected subjects were conducted. Results from these interaction studies and other potentially significant drug interactions are prominently displayed in the package insert. As with other PIs, the LPV/RTV label includes warnings and precautions for new onset diabetes, hyperglycemia, increased bleeding episodes in patients with hemophilia and fat redistribution.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Statistics and/or Other Consultant Reviews

CMC: No new chemistry and manufacturing data were submitted with this sNDA. Please refer to the original NDA reviews for background information.

Animal Pharmacology and Toxicology: Abbott updated the Carcinogenesis, Mutagenesis and Impairment of Fertility Section of the package insert based on the Week 104 mice and rat data. The Division requested these changes as outlined in the October 29, 2003 correspondence. Please refer to the Pharmacology/Toxicology review for details. In summary, an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma were observed in both male and female mice and male rats at doses that produced approximately 1.6 – 2.2 times (mice) and 0.5 times (rats) the human exposure. We do not know how predictive the results of the rodent carcinogenicity studies may be for humans. Of note, LPV and RTV are not mutagenic or clastogenic in a battery of in vitro and in vivo assays.

Microbiology: No new information regarding the development of resistance or baseline genotype and phenotype and virologic outcome were observed. Please refer to sections 1.6 and 2.6 for a summary of the clinical virology data.

Clinical Pharmacology: Results from a multiple dose study in HIV and HCV co-infected subjects with mild to moderate hepatic impairment were submitted for review. Data from this trial fulfills the postmarketing commitment 9. Please refer to the Clinical Pharmacology review for details. In summary, no dose adjustments are required for subjects with mild to moderate hepatic impairment.

Statistics: This review is a joint clinical/statistical review. Information from the statistical review performed by Dr. Rafia Bhore are incorporated into Section V – Integrated Review of Efficacy.

III. Description of Clinical Data and Sources

A. Overall Data

This submission contains data collected from two phase I/II dose finding studies M97-720 and M97-765. In addition, data from a multiple dose study in HIV and HCV co-infected subjects with mild to moderate hepatic impairment were submitted to support changes in the package insert and to fulfill postmarketing commitment #9.

B. Tables Listing the Clinical Trials

The following table lists the clinical trials submitted in this supplement

Study Number	Subject Population (N)	Doses Studied/Control Arm	Design	Endpoints
M97-720	Naïve (N=100)	200/100 + d4T + 3TC 400/100 + d4T + 3TC 400/200 + d4T + 3TC	Randomized, Open-Label, Dose Ranging	Proportion < 400 and 50 copies/mL
M97-765	Experienced (N=70)	400/100 + NVP +RTIs 400/200 + NVP +RTIs	Blinded, Randomized, Dose Ranging	Proportion < 400 and 50 copies/mL

C. Postmarketing Experience

Recently, reports of serious skin reactions were identified in the Early Access Program (EAP) and in the Kaletra once daily versus twice daily clinical trial. With the exception of exfoliative dermatitis, severe rashes following use with LPV/RTV are not mentioned in the package insert. As a result, we requested a consult review from the Office of Drug Safety (ODS) regarding postmarketing reports of serious skin reaction with the use of LPV/RTV, specifically, Stevens Johnson Syndrome (SJS) and erythema multiforme. Please refer to Appendix B for a copy of the ODS consult review. Based on the information contained in the ODS consult review, SJS and erythema multiforme were added to the Adverse Reaction: Post-marketing experience section of the package insert.

D. Literature Review

Literature reviews were not provided by Abbott. ODS conducted a literature review for all skin reactions. Please refer to Appendix B for a copy of the ODS consult review.

IV. Clinical Review Methods

A. How the Review was Conducted and Overview of Materials Consulted in Review

This is a joint statistical/clinical review based on the evaluation of NDA sections 8, 11 and 12 and includes the 204-week study report for M97-720. The Week 144 study report for M97-765 was submitted to IND 51,715 on June 28, 2002 and March 9, 2004 (serial submission 619 and 692, respectively). Electronic data provided as review aids were included for study M97-765. The safety and efficacy analyses were confirmed by independent FDA analyses of the data. Results from Dr. Rafia Bhore's Biometrics review are incorporated in Section V – Integrated Review of Efficacy.

For this review the efficacy (HIV RNA and CD4) data, adverse events, and laboratory data were reviewed in detail. We used JMP Statistical Discovery and SAS software to evaluate the efficacy and safety data. The results from the original NDA were reviewed and differences between the Week 72 data from that report and the Week 144 or 204 data were compared and highlighted in this review.

Minor differences between Abbott's and FDA's analyses for efficacy and safety were noted. The differences had no impact on the overall conclusions.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits were not requested for this application. DSI audits were made for the original NDA for the phase III studies. Only minor violations were noted at that time and did not affect the quality of the data submitted.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

All study protocols were written to conform to accepted ethical standards and were reviewed and approved by Institutional Review Boards overseeing each investigative site prior to enrollment of subjects.

D. Evaluation of Financial Disclosure

Studies M97-720 and 765 were phase I/II, non-pivotal studies; therefore, investigators were not required to disclose proprietary interest or significant equity as required under 21 CFR 54.

V. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Through four years of follow-up, antiretroviral-naïve subjects receiving LPV/RTV achieved and maintained durable HIV RNA suppression and significant increases in CD4 cell counts. At Week 204, 71% and 70% of subjects achieved HIV RNA < 400 copies/mL and < 50 copies/mL, respectively. In addition, statistically significant increases in CD4 cell counts were observed for all subjects at each study visit. The mean change from baseline at Week 204 was 440 cell/mm^3.

In antiretroviral-experienced subjects, more than 50% achieved HIV RNA < 400 copies/mL at Week 144. The 400/100 mg and 400/200 mg dose groups were comparable with respect to virologic and immunologic response.

B. General Approach to Review of the Efficacy of the Drug

In general, for phase III studies, the Division evaluates the proportion of subjects with HIV RNA < 400 copies/mL or 50 copies/mL as the primary measure of the efficacy at Week 24. For controlled trials of 48 weeks or longer in duration, the "Time to Loss of Virologic Response (TLOVR)" is evaluated and results are displayed in package inserts. The TLOVR definition includes responders as subjects maintaining a minimum of two sequential HIV RNA measurements below the limit of assay detection without intervening replicated rebounds or treatment discontinuations.

For the original NDA review for studies M97-720 and M97-765, the proportion of subjects with HIV RNA < 400 copies/mL and < 50 copies/mL at Week 72 were evaluated and the results are displayed in the package insert in text. TLOVR analyses were not conducted or presented for these Phase I/II trials since these trials were considered supportive; therefore, limited summary results are displayed in the package insert. For this clinical review, the efficacy section focuses on the proportion of subjects with HIV RNA < 400 copies/mL and < 50 copies/mL. Please refer to the statistical review for additional analyses.

C. Detailed Review of Trials by Indication

1. Clinical Trial M97-720 (720) "Phase I/II Study of LPV/RTV in Combination with Reverse Transcriptase Inhibitors in Antiretroviral Naïve HIV-Infected Subjects"

1.1 Study Design and Study Population

This was a randomized, multi-center study of LPV/RTV in combination with stavudine (d4T) and lamivudine (3TC) in HIV-infected subjects. Thirty-two antiretroviral-naïve subjects with HIV RNA ≥ 5,000 copies/mL were randomized in group I to receive one of the following blinded treatment arms:

Group I:

LPV/RTV 200/100 mg BID + d4T + 3TC
LPV/RTV 400/100 mg BID + d4T + 3TC

D4T and 3TC were added on day 22.

Following a safety review after four weeks of dosing by the first 16 subjects in group II, 68 subjects were randomized to one of the following blinded treatment arms.

Group II:

LPV/RTV 400/100 mg BID + d4T + 3TC
LPV/RTV 400/200 mg BID + d4T + 3TC

D4T and 3TC were given on Day 1 in group II.

All subjects continuing on treatment at Week 48 were converted to open-label LPV/RTV 400/100 mg between Weeks 48 and 72.

1.2 Endpoints

Primary Efficacy Outcome Measure

The primary efficacy outcome measure was proportion of subjects with HIV RNA < 400 copies/mL at Week 24 and the duration of response through Week 48. For the long-term follow-up analyses, the primary endpoint was extended to Week 204.

Secondary Efficacy Outcome Measure

Secondary efficacy variables included the following:

- proportion of subjects with viral load below the limit of assay quantification (LOQ) at each visit
- proportion of subjects who did not experience loss of virologic response by Week 24,
- change from baseline to each visit
- the time-normalized area under the curve minus baseline (AAUCMB) through Weeks 16, 24, and 48 for HIV RNA, CD4, and CD8

Again, for the long-term follow-up analyses, these endpoints were extended to Week 204.

1.3 Analysis Plan

The following describes Abbott's analysis plan for this study.

The primary efficacy variable was the proportion of subjects with viral load below the LOQ at Week 24 and the time to loss of virologic response through Week 48. Analyses

of the proportion of subjects with viral load below the LOQ were performed at Weeks 48, 72, and 204 as well; statistical significance was determined using Fisher's exact test. The primary analysis was performed after all eligible subjects had completed 48 weeks of study therapy. Time to Loss of Virologic Response was determined using Kaplan-Meier methodology. Secondary efficacy variables included:

- Proportion of subjects with viral load below the LOQ at each visit.
- Proportion of subjects who did not experience loss of virologic response by Week 24.
- Change from baseline to each visit in HIV RNA, CD4, and CD8.
- AUCMB through Weeks 16, 24, and 48 for HIV RNA level, CD4 cell count, and CD8 cell count.

The change from baseline and the AUCMB analyses were performed using a one-way analysis of variance (ANOVA). Baseline was defined as the mean of the last two measurements prior to the first dose of study drug. Efficacy analyses for this interim report were performed on all data collected during the first 204 weeks of the study.

1.4 Study Population

In general, baseline characteristics for all randomized subjects were comparable between treatment regimens. The study population was predominately male (96%) and had a mean age of approximately 35 years. Non-white racial groups comprised 30% of the population.

The median baseline HIV RNA level for all randomized subjects was 4.92 $\log_{10}$ copies/mL and was comparable between treatment regimens. Forty-five percent of subjects had baseline HIV RNA levels ≥ 100,000 copies/mL. The median baseline CD4 cell count was 326 cells/mm^3.

The table below summarizes subject characteristics at baseline.

Demographic Data

	Group I		Group II	
	200/100 mg BID	400/100 mg BID	400/100 mg BID	400/200 mg BID
Number of Subjects	16	16	35	33
Mean age, Yrs	36	33	35	35
Men	100%	88%	97%	97%
Race or Ethnicity Caucasian Black or African American	 75% 25%	 69% 31%	 74% 26%	 64% 36%
Baseline mean plasma HIV RNA (PCR), $\log_{10}$ copies/mL	4.88 (3.7 – 5.9)	4.96 (3.7 – 6.1)	4.78 (3.3 – 6.1)	4.97 (3.9 – 6.7)
Number of subjects with baseline HIV RNA > 100,000 copies/mL	8 (50%)	8 (50%)	14 (40%)	15 (45%)
Baseline median CD4 cell count (cells/mm^3)	471	330	343	275

1.5 Subject Disposition

At total of 107 subjects were randomized and 100 subjects received at least one dose of LPV/RTV. Overall, 51 subjects received the 400/100 mg BID dose. Of note, all subjects ongoing at Week 48 were converted to open-label LPV/RTV 400/100 mg bid between Weeks 48 and 72. Conversion to the 400/100 mg dose was mostly completed between the Week 48 and Week 60 visits.

In the original NDA review, 13% of all subjects who received at least one dose of study drug discontinued treatment at or before Week 72, including four subjects who prematurely

discontinued study due to an adverse event (AE). Through year four, 28% of subjects discontinued study at or before Week 204. A total of nine subjects prematurely discontinued due to an AE or HIV-related event. The table below summarizes the subject disposition by original randomized treatment and overall study population.

Subject Disposition Though Week 204

Original Assignment	Group I		Group II		Overall	
	200/100 BID	400/100 BID	400/100 BID	400/200 BID	400/100 BID	All Doses
Received at least one dose of study medication	16	16	35	33	51	100
Discontinued at or before year 4	5 (31%)	4 (25%)	7 (20%)	12 (36%)	11 (22%)	28 (28%)
Personal reasons	0	0	1	0	1	1
Death	0	0	1	0	1	1
AE/HIV related event	3	1	2	3	2	9
Subject noncompliant	1	0	1	3	1	5
Lost to follow-up	1	2	1	4	2	8
Other	0	1	1	2	3	4

1.6 Efficacy Endpoint Outcomes

The proportion of subjects with HIV RNA values < 400 copies/mL (and < 50 copies/mL) and the mean change from baseline for CD4 cell counts are summarized in the tables below by original treatment assignment. These analyses were based on the intent-to-treat (ITT) population which consisted of all subjects who were randomized and received at least one dose of the study drug LPV/RTV.

For the efficacy endpoint of proportion of subjects achieving HIV RNA values <400 copies/mL (and <50 copies/mL) we performed two kinds of analyses. The analysis shown in the first table below is based on the FDA Time to Loss of Virologic Response (TLOVR) algorithm which gives the success status of patients through 204 weeks of treatment. The TLOVR algorithm accounts for data at each visit through 204 weeks. According to this algorithm, if a patient is suppressed virologically without discontinuing therapy or adding new drugs, then the patient is classified as a success regardless of whether a CDC Class C event occurred or not. The second analysis is based on a snapshot of the efficacy results at a given visit where missing data for any reason at the specified visit was considered > 400 HIV RNA copies/mL, i.e., ITT analysis with missing=failure.

In Group I, patients and study personnel were blinded to the dose of lopinavir (200 mg or 400 mg), while in Group II, patients and study personnel were blinded to the dose of ritonavir (100 mg or 200 mg) during the first 48 weeks for all patients. Note that after Amendment 5 of the protocol was approved by the IRB, the blinded phase of the study ended and the LPV/RTV 400/100 mg dose was chosen. All subjects who were ongoing after Week 48 were converted from their randomized double-blind dose of LPV/RTV to open-label LPV/RTV 400/100 mg bid between Weeks 48 and 72.

The TLOVR algorithm results showed that the proportion of patients with HIV RNA <400 copies/mL through 204 weeks in Group I receiving the LPV/RTV 200/100 mg bid dose was 69% and those receiving LPV/RTV 400/100 mg bid dose was 75%. These two numbers were not statistically significantly different with p-value=0.694. Similarly, the discontinuations due to

adverse events or other reasons were not statistically significantly different. Through 204 weeks of treatment there was no significant difference in efficacy between patients who received LPV/RTV 200/100 mg or LPV/RTV 400/100 mg in the first 48 weeks was observed.

Efficacy Outcomes of Randomized Treatment Through Week 204 in KALETRA™ Study M97-720 (Antiretroviral treatment-naïve patients) using FDA Time to Loss of Virologic Response (TLOVR) Algorithm

Outcome	Group I				Group II					
	LPV/RTV 200 mg (blinded) / 100 mg +d4T +3TC (N=16)		LPV/RTV 400 mg **(blinded)** / 100 mg +d4T +3TC (N=16)		LPV/RTV 400 mg / 100 mg **(blinded)** +d4T +3TC (N=35)		LPV/RTV 400 mg / 200 mg (blinded) +d4T +3TC (N=33)		**Overall**	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Responder*[1] (<400 copies/mL)	**11**	**69%**	**12**	**75%**	**28**	**80%**	**20**	**61%**	**71**	**71%**
Virologic Failure[2]	**1**	**6%**	**1**	**6%**	**1**	**3%**	**4**	**12%**	**7**	**7%**
Rebound	1	6%	1	6%	1	3%	4	12%	7	7%
Death	–	–	–	–	**1**	**3%**	–	–	**1**	**1%**
Discontinued due to adverse events	**3**	**19%**	**1**	**6%**	**2**	**6%**	**3**	**9%**	**9**	**9%**
Discontinued due to other reasons[3]	**1**	**6%**	**2**	**13%**	**3**	**9%**	**6**	**18%**	**12**	**12%**
Consent withdrawn (Personal reasons)	0	0%	0	0%	1	3%	0	0%	1	1%
Loss to follow	1	6%	1	6%	1	3%	3	9%	6	6%
Non-compliance	0	0%	0	0%	0	0%	2	6%	2	2%
Other	0	0%	1	6%	1	3%	1	3%	3	3%
Total	16		16		35		33		100	
95% Confidence Interval on Success Rates	(46%, 92%)		(54%, 96%)		(67%, 93%)		(38%, 72%)		(62%, 80%)	
95% Confidence Interval on difference in proportions	(-37%, 25%)				(-2%, 41%)					
p-value on difference in proportions	0.694				0.079					

Percentages are based on the total number of subjects in corresponding treatment group.

* Corresponds to rates at Week 48 in Figure.

NOTE 1: A total of 161 patients were enrolled in Study M97-720 out of which 100 patients were randomized and received at least one dose (ITT population).

NOTE 2: Six patients in Study 720 had rebound and subsequently resuppressed virologically. These patients were counted as successes in this analysis

1 Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 204.

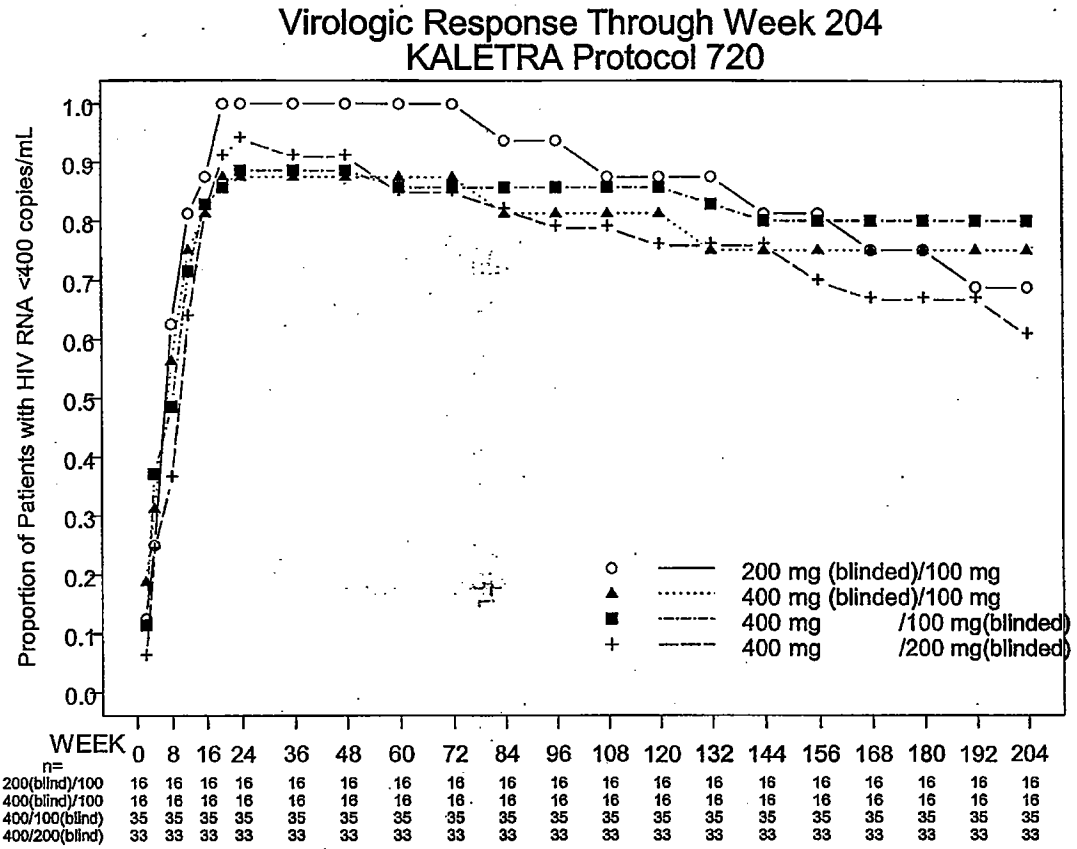
2 Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 204.

3 Includes loss to follow-up, patient's withdrawal, non-compliance, and other reasons.

Source: FDA Statistical Reviewer's analysis.

In Group I, only 16 patients per treatment group were randomized. In comparison, Group II had 35 and 33 patients per group. The proportion of patients with HIV RNA <400 copies/mL through 204 weeks was 80% among patients receiving LPV/RTV 400/100 mg bid and was numerically higher than those patients receiving LPV/RTV 400/200 mg bid (61%). This difference between the two groups was marginally significant with p-value = 0.079 and is also seen in the graph shown below where the proportion of successes in the 400/200 mg bid group is consistently

numerically lower beyond 48 weeks through 204 weeks as compared to those patients who were randomized to 400/100 mg from the beginning.



WEEK	0	8	16	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204
n=																			
200(blind)/100	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16
400(blind)/100	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16
400/100(blind)	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35
400/200(blind)	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33	33

Source: FDA Statistical Reviewer's analysis

The efficacy results (proportion of patients with HIV RNA <400 copies/mL) based on the TLOVR algorithm through 204 weeks was identical to the results based on the second snapshot analysis of ITT (missing = failure) at Week 204 across all treatment groups (69%, 75%, 80%, and 61% for 200/100 mg bid , 400/100 mg bid, 400/100 mg bid, and 400/200 mg bid doses, respectively). The second analysis is shown in table below.

Recall that all subjects started receiving LPV/RTV 400/100 mg bid between Weeks 48 and 72. Through 204 weeks of treatment, over 85% of the 125,000 subject-days of dosing in the study were at the 400/100 mg dose. Results for all dose groups were combined and are presented in the package insert. The rationale for this decision was the following:

- The original objective of the study was to determine a dose for phase III studies. After dose selection, the objective of the study was to collect long-term safety and efficacy for the 400/100 mg dose.
- The study achieved the objective to collect long-term safety and efficacy for the 400/100 mg dose. Subjects randomized to 200/100 mg or 400/200 mg received this dose for approximately 48 weeks and received 400/100 mg for approximately 3 years.

The possibility exists that subjects randomized to the highest dose group (400/200 mg) may have a greater virologic response thereby overestimating the overall response rate for all dose groups combined. However, in fact, the 400/200 mg dose group had the lowest response rate at Weeks

48 and 72 (73%, compared to 81-100%). The lower response rate seen for the 400/200 mg group may be due in part to tolerability issues. Also, fewer subjects randomized to the 400/200 mg group had HIV RNA < 400 copies/mL at Week 204 compared to the 400/100 mg group (61% versus 78%). Furthermore, response rates for all dose groups combined were lower than the 400/100 mg dose groups (71% versus 78%). The inclusion of all subjects for the final analyses is a conservative approach and did not overestimate the virologic response rates in the study as reported above.

Proportion of subjects with HIV RNA < 400 copies/ml (< 50 copies/mL)
ITT Analysis (Missing=Failure)

Received at least one dose of study medication	Group I		Group II		Overall	
	200/100 BID	400/100 BID	400/100 BID	400/200 BID	400/100 BID	All Doses
	N=16	N=16	N=35	N=33	N=51	N=100
Week						
24	81% (69%)	81% (75%)	89% (74%)	91% (67%)	84% (75%)	87% (71%)
48	100% (100%)	81% (56%)	92% (86%)	73% (64%)	88% (76%)	85% (76%)
72	88% (81%)	69% (69%)	86% (83%)	82% (70%)	80% (78%)	82% (76%)
144	81% (69%)	75% (63%)	80% (80%)	70% (67%)	78% (75%)	76% (71%)
204	69% (69%)	75% (75%)	80% (80%)	61% (58%)	78% (78%)	71% (70%)

Statistically significant increases in CD4 cell counts were seen for all subjects at all study visits. The mean change from baseline at Week 204 was 440 cells/mm^3. Changes in CD4 cell counts were consistent regardless of the baseline CD4 cell count value. The results of this study show durable suppression of HIV RNA and increases in CD4 cell counts in antiretroviral-naïve subjects.

Mean Change from Baseline in CD4 Cell count (cells/mm^3)

	Group I		Group II		Overall	
	200/100 BID	400/100 BID	400/100 BID	400/200 BID	400/100 BID	All Doses
Received at least one dose of study medication	N=16	N=16	N=35	N=33	N=51	N=100
Week						
24	142	199	141	172	159	161
48	208	277	227	200	243	223
72	269	342	217	264	255	260
144	484	505	282	348	352	373
204	694	514	374	367	415	440

New AIDS-defining events:

Subjects who experienced a new AIDS defining event during the study were reviewed in detail. Subjects who experienced a new AIDS defining event (as defined by the 1993 CDC classification system) were included in the analyses if the event was not present at baseline or noted in the medical history and occurred after at least 7 days of receiving study drug. New AIDS-defining events occurred in five subjects in study M97-720 and included events of lymphoma, MAI, HIV-

wasting and Kaposi's sarcoma. These events were reviewed in the original NDA. No new AIDS-defining events were observed during weeks 72-204.

Resistance

Genotypic results were available for 11/16 subjects who experienced a loss of virologic response at or prior to Week 204. Genotypic results were not available for five subjects primarily due to low HIV RNA copy number (499 – 577). All five of these subjects maintained HIV RNA < 400 copies/mL through Week 204.

Abbott states none of the 11 subjects exhibited genotypic resistance to lopinavir as defined by the emergence of a primary or active site mutation at positions 8, 30, 32, 46, 47, 50, 82, 84 or 90. Our review found one subject (113) who developed the M36M/I mutation on study days 1092 and 1271. In other PI-experienced studies the M36 mutation was associated with decreased response rates in subjects receiving LPV/RTV based regimens. In a previous correspondence to Abbott, we requested inclusion of changes at amino acid residues 33, 36, 41, 62, 64 and 93 in the resistance definition. Mutations at positions 33, 36, 41, 62, 64 and 93 were observed in treatment-naïve subjects who experienced increases in HIV RNA during treatment and in some instances shifts in susceptibility.

As previously mentioned, subject 113 developed the M36M/I mutation and experienced a loss of virologic response during study visits 504 – 765 (HIV RNA range 575 – 9177copies/mL). On visits 840 and 924 the HIV RNA was 284 and 182 copies/mL, respectively. During study visits 1008 – 1280 the HIV RNA values fluctuated between 400 and 3771 copies/mL, followed by a confirmed resuppression on days 1344 and 1428 (HIV RNA 134 copies/mL and 288 copies/mL, respectively). Subject 113 did not develop a large viral rebound despite development of the M36 mutation. The fluctuation in HIV RNA may be a consequence of intermittent adherence to treatment. The lack of a sustained viral rebound may also be due to the amino acid mixture (M/I) at position 36.

For the remaining subjects mutations at positions L63LP, R57R/K and V3I developed. Mutation L63L/P is a known polymorphism. The clinical significance of the remaining two mutations R57R/K and V3I are unknown at this time.

Two subjects developed the M184V mutation. Subject 113 developed the M184V mutation in conjunction with the M36 mutation. The M184V mutation was detected at study visit 333 in subject 220; however, no baseline genotype was available for this subject. As a result, we cannot determine if this mutation was also present at baseline or if this mutation developed during treatment.

2. **Clinical Trial M97-765** "Randomized, multi-center study of LPV/RTV in combination with two nucleoside reverse transcriptase inhibitors and nevirapine in protease inhibitor experienced HIV-infected males and females"

2.1 Study Design and Subject Population

This was a blinded, randomized, multi-center trial in seventy antiretroviral-experienced subjects with HIV RNA levels between 1,000 and 100,000 copies/mL. Subjects were:

- NNRTI naïve
- naïve to at least one NRTI
- currently receiving a PI and one or two NRTIs that had not changed in the last 12 weeks prior to enrollment

Subjects were randomized to one of the following dose groups:

Group 1: LPV/RTV 400/100 mg BID
Group 2: LPV/RTV 400/200 mg BID

The PI in each subject's existing regimen was discontinued on day –1. For days 1-14, subjects received their assigned LPV/RTV regimen in combination with the RTIs received in their existing regimen. The study was designed in this manner to isolate the effect of LPV/RTV on HIV RNA reduction over two weeks. On Day 15, each subject received a new RTI regimen that included at least one new RTI not previously received. Nevirapine was also added to each subject's regimen on Day 15.

2.2 Endpoints

The primary efficacy outcome measure was the proportion of subjects with HIV RNA < 400 copies/mL at Week 24 and the Time to Loss of Virologic Response.

2.3 Study Population

Seventy subjects were randomized and received at least one dose of study medication. In general, baseline characteristics for all randomized subjects were comparable between treatment regimens. The study population was predominantly male (90%) and had a mean age of approximately 40 years. Non-white racial groups comprised 27% of the population.

The median baseline HIV RNA level for all randomized subjects was 4 $\log_{10}$ copies/mL and was comparable between treatment regimens. The median baseline CD4 cell count was 371 cells/mm^3.

The table below summarizes subject characteristics at baseline.

Demographic Data

	400/100 mg	400/200 mg
Number of Subjects	36	34
Mean Age, Yrs	41	40
Men	34 (94%)	29 (85%)
Race or Ethnicity		
Caucasian	29	22
Black or African American	7	10
Asian/Pacific Islander	0	2
Baseline Antiretroviral Therapy		
RTI:		
DDI	7 (19.4%)	0
3TC	28 (77.8%)	33 (97.1%)
d4T	22 (61.1%)	17 (50%)
ZDV	14 (38.9%)	16 (47.1%)
PI:		
Amprenavir	1 (2.8%)	0
Indinavir	15 (41.7%)	16 (47.1%)
Nelfinavir	14 (38.9%)	11 (32.4%)
Ritonavir	1 (2.8%)	3 (8.8%)
Saquinavir	5 (13.9%)	4 (11.8%)
Baseline mean plasma HIV RNA (PCR), log_{10} copies/mL	4.1	4.0
Baseline median CD4 cell count (cells/mm^3)	371	372

Baseline phenotypic data were available for 57/70 (81%) subjects. Sixty-three percent of subjects were phenotypically resistant to their baseline PI. Phenotypic resistance was defined as $\geq$ 4 fold increase in EC_{50} relative to wild type virus. Also, 32% of subjects were cross-resistant to at least three of the four PIs licensed at the time the study was conducted.

Number of Subjects with Changes in Phenotypic Susceptibility

Baseline PI	Fold-Change in EC_{50} to Baseline PI (Relative to Wild Type)			
	< 4 fold change	$\geq$ 4 fold change	Mean Change	Range
Indinavir (n=24)	8	16	7.4	0.4 – 26
Nelfinavir (n=21)	8	13	19.1	0.8 – 54.2
Saquinavir (n=9)	5	4	9.5	0.7 – 32.4
Ritonavir (n=3)	3	0	23	1.4

2.4 Subject Disposition

A total of 74 subjects were randomized and 70 subjects received at least one dose of LPV/RTV. Thirty-six subjects received LPV/RTV 400/100 mg bid and 34 subjects received LPV/RTV 400/200 mg bid.

In the original NDA review, seven and six subjects in the 400/100 and 400/200 groups, respectively, discontinued treatment at or before Week 72. Four subjects prematurely

discontinued study due to an adverse event/disease progression (3 in the 400/100 group vs 1 in the 400/200 group). Through Week 144, 39% of subjects prematurely discontinued study (400/100 mg: 14 subjects and 400/200 mg: 13 subjects). Six subjects in each group discontinued prior to the Week 48 visit, one subject in the 400/100 mg group discontinued between Weeks 48 and 72 and seven subjects in each dose group discontinued between Weeks 72 and 144. The table below summarizes the subject disposition by original randomized treatment and overall study population.

Subject Disposition Through Week 144

Original Assignment	400/100 mg	400/200 mg
Received at least one dose of study medication	36	34
Number of Subjects completing study	22	21
Premature Discontinuations	14	13
Personal Reasons	2	0
Death	0	2
AE/HIV-related event	5	4
Subject noncompliant	1	1
Lost to follow-up	1	2
Other (virologic failure)	2	0
Other (misc)	3	4

2.6 Efficacy Endpoint Outcomes

No statistically significant differences were observed between the dose groups for the analyses of proportion < 400 copies/mL or < 50 copies/mL. The intent-to-treat analyses where missing data were counted as > 400 (or > 50) copies/mL are presented in the table below. Of note, the efficacy results observed in this study are based on a select patient population. Subjects were PI experienced and NNRTI naïve. All subjects received an NNRTI (nevirapine) in combination with a new PI (LPV/RTV). As a result subjects received at least two new active agents. Nevertheless, more than half of the subjects achieved and maintained HIV RNA < 400 copies/mL at Week 144.

Proportion of subjects with HIV RNA < 400 copies/mL (< 50 copies/mL) ITT analysis (Missing = Failure) – Week 144

	400/100 BID mg	400/200 BID mg
Received at least one dose of study medication Week	36	34
48	67%	74%
72	75% (58%)	71% (53%)
144	53% (47%)	56% (53%)

Of note, significant differences in baseline phenotypic susceptibility to LPV/RTV were seen between the two dose groups. Mean fold change in EC_{50} to LPV/RTV relative to wild type virus was 1.7-fold for the 29 viral isolates from subjects in the 400 mg/100 mg dose group and 3.9-fold for the 30 viral isolates from subjects in the 400 mg/200 mg dose group (p=0.083). Additionally, a higher percentage of subjects in the 400 mg/200 mg dose arm demonstrated baseline viral isolates with a ≥four-fold increase in EC_{50} to LPV/RTV relative to wild type virus compared to subjects in the 400 mg/100 mg dose arm (30% vs. 7%; p=0.04).

Abbott also evaluated the proportion of subjects with HIV RNA < 400 and < 50 copies/mL by baseline HIV RNA (< 10,000 or > 10,000 copies/mL). The results of the analyses were confirmed by FDA. For subjects with baseline HIV RNA < 10,000 copies/mL, no statistically significant differences were observed between dose groups for HIV RNA < 400 or < 50 copies/mL. For the subjects with baseline HIV RNA > 10,000 copies/mL sporadic statistically significant differences were seen at Weeks 12, 16, and 20 but no significant difference were seen between Weeks 24 and 144 for HIV RNA < 400 copies/mL. A trend was seen towards a higher proportion of subjects with baseline HIV RNA > 10,000 copies/mL in the 400/200 mg group having < 50 copies/mL compared to the 400/100 mg dose arm. The Week 144 results by baseline HIV RNA are presented below.

Proportion < 400 copies/mL (< 50 copies/mL) by baseline HIV RNA
ITT analysis (Missing = Failure) – Week 144

HIV RNA	400/100 BID	400/200 BID
< 10,000 copies/mL	60% (55%)	53% (47%)
> 10,000 copies/mL	44% (38%)	59% (59%)

Statistically significant increases in CD4 cell counts were observed for both dose groups compared to baseline through Week 144. The mean increase from baseline was 177 cells/mm^3 and 249 cells/mm^3 for the 400/100 mg and 400/200 mg dose groups, respectively.

In addition, no new AIDS-defining events were observed in study M97-765.

Overall, through 144 weeks of treatment, both 400/100 mg and 400/200 mg bid, when combined with a NNRTI and NRTIs, were effective in suppressing HIV RNA and increasing CD4 cell counts. As stated previously, a trend was seen towards a higher proportion of subjects with baseline HIV RNA > 10,000 copies/mL in the 400/200 mg group having < 50 copies/mL compared to the 400/100 mg dose arm. This difference was not statistically significant. The results of the trial are based on a small population (n=70) and the study was not powered to detect statistical differences between the dose groups. Abbott has an outstanding phase IV commitment to evaluate the activity of higher doses of LPV/RTV in subjects exhibiting virologic failure or showing reduced susceptibility to multiple PIs. Nevertheless, subjects receiving LPV/RTV 400/100 mg bid in combination with a NNRTI and NRTIs achieved and maintained an adequate virologic response through 144 weeks of treatment.

Resistance

Several genotypic and phenotypic analyses were conducted by FDA from subjects treated with LPV/RTV 400/100 mg bid. The relationship between baseline mutations and phenotypic susceptibility and virologic outcome were assessed. In addition, the resistance profile for subjects with virologic failure was evaluated. The analyses conducted are based on the as-treated population for the 400/100 mg bid dose group and included 28 subjects from study M97-765. Because the subgroups for primary PI-associated mutations were small, we were not able to reach definitive conclusions to further characterize the impact of baseline mutations on virologic outcome.

The results from the 28 subjects in study M97-765 are not contradictory to the information currently in the label. The clinical virology information currently in the LPV/RTV label includes data from M98-975, a study of subjects who experienced multiple (2 or more) PI failures, but who were NNRTI naive. Given the limited number of subjects we are not able to identify lopinavir-associated mutational patterns. In addition, the phenotypic results from M97-765 did not provide any additional information. Currently the label includes data based on three baseline lopinavir susceptibility break-points < 10 fold, > 10 and < 40 fold and ≥ 40 fold. The median baseline lopinavir susceptibility was 1.38 fold (range 0.47 – 8.4). The Division requests Abbott to submit

resistance datasets according to the Division's HIV resistance template from the three treatment-experienced studies (M97-765, M98-975 and M98-888) in order to further characterize the impact of baseline mutations and virologic outcome.

VI. Integrated Review of Safety

A. Brief Statement of Conclusions

Based on the data submitted for antiretroviral-naïve and antiretroviral-experienced subjects, LPV/RTV in combination with other ARVs, had an acceptable safety profile through 144-204 weeks of treatment. The overall safety profile of LPV/RTV was similar to other PIs approved for the treatment of HIV infection. The rate and pattern of AEs and laboratory abnormalities were not markedly different from those identified in the original and supplemental NDAs.

The most commonly reported AEs observed in the two trials were related to GI disorders, including diarrhea/abnormal stools and nausea. Overall, 10% of subjects discontinued study due to an AE or HIV-related event. AEs leading to study discontinuation were consistent with the AE profile of the study medications used in the trials. The type and incidence of laboratory abnormalities observed were similar to those seen with other ARVs. With the exception of lipids, laboratory abnormalities did not appear to increase over time. Overall, no new or unexpected safety findings were observed in studies M97-720 or M97-765.

Although not new, additional cases of serious skin reactions were reported through the Adverse Event Reaction System (AERS), leading to the addition of Stevens Johnson Syndrome and erythema multiforme events to the Adverse Reaction section of the package insert.

B. Description of Subject Exposure

In study M97-720, the median time on study medication (at any dose) was 1472 days (22-1472). The median and maximum duration of exposure to study medication were similar between the dose regimens and between Groups I and II.

In study M97-765 the median time on study medication was approximately 1,087 days (1-1176) for both groups.

C. Methods and Specific Findings of Safety Review

Studies M97-720 and M97-765 were conducted in treatment-naïve and treatment-experienced subjects to evaluate the safety and efficacy of three dose regimens of LPV/RTV in combination with other ARVs. The studies were designed to determine a dose for phase III trials. Given the different patient populations enrolled, the two studies were reviewed separately. Where applicable, the results of these studies were compared to the results from the original and supplemental NDAs to determine if any new or unexpected toxicities were observed with long-term dosing.

The safety analyses include all subjects who received at least one dose of study medication. The safety database for the antiretroviral-naïve study included 100 subjects, of whom 51 subjects were originally randomized to receive the approved dose regimen of 400/100 mg bid. The safety database for the antiretroviral-experienced study is 70 subjects, of whom 36 received 400/100 mg bid.

Adverse event and laboratory data were collected for each subject at the protocol defined study visit. AEs and laboratory abnormalities were graded according to a modified ACTG toxicity grading scheme. Investigators assigned a severity grade and relationship to study drug. SAEs were collected in accordance with regulations and include those events which resulted in death, life-threatening situation, hospitalization (or prolonged), persistent or significant disability, congenital anomaly or other medically important event. The AEs were grouped by body system. Laboratory abnormalities resulting in AEs and events associated with fat redistribution are discussed separately and not displayed in the overall AE summary.

The study reports include tabular summaries of AEs, evaluation of changes over time in laboratory abnormalities and all grades of laboratory abnormalities. Abbott's analyses and conclusions were independently confirmed by FDA's review. In general, the FDA analysis of the safety data confirmed Abbott's findings. Minor differences between the two analyses were noted; however, the differences did not affect the overall results and conclusions.

C.1. General Adverse Events

All subjects in studies M97-720 and M97-765 experienced at least one AE during the treatment period. In both studies the most commonly reported AE were related to GI disorders, including diarrhea, nausea and abnormal stools. A list of AEs of at least moderate severity and of probable, possible or unknown relationship is presented in the table below. Appendix A contains a list of all AEs regardless of severity or causality.

M97-720

GI disorders were generally mild to moderate in severity and probably or possibly related to LPV/RTV use. Five subjects reported severe GI events. Only one subject prematurely discontinued from the study due to a GI event (increased transaminases).

In addition to the GI disorders, rhinitis, pharyngitis, headache, infection and pain were also commonly reported AEs. Rash was observed in 40% of the subjects in this study; however, the majority of the cases were mild and commonly attributed to contact or HIV dermatitis and fungal or bacterial infections.

Severe AEs, regardless of causality, were reported in 39 subjects, of which 13 subjects reported 14 drug-related severe AEs. The drug-related severe AEs included GI events (n=5), abnormal LFTs (n=4), and one event each of asthenia, hyperlipemia, hypothyroidism/hypogonadism/hepatitis, diabetes mellitus and death. Only one subject with a severe AE discontinued study. This subject had abnormal LFTs and a history of hepatitis C infection. Reports of LFT abnormalities, hepatitis and diabetes are further discussed in the AE of interest section and laboratory abnormality sections.

Overall, the toxicity profile observed is consistent with other LPV/RTV trials. No new or unexpected AEs were observed. Treatment with LPV/RTV was generally well-tolerated over 4 years of treatment.

M97-765

In addition to GI disorders, rhinitis, cough increased, infection, headache, pain, pharyngitis, rash and asthenia were also commonly reported AEs in both dose groups. The incidence of AEs was similar between the dose groups with the following exceptions. More subjects in the 400/200 mg group experienced obesity and sweating. Treatment-related obesity was reported in approximately 15% of subjects in the 400/200 mg group compared to no subjects in the 400/100 mg group. Interesting, all events were described as abdominal fat accumulation, a known AE for antiretroviral therapy. The incidence of sweating was statistically significantly greater in the 400/200 mg group (29% vs 8%). Twelve of the 13 cases were not considered related to LPV/RTV by the investigator. Alternative etiologies included concurrent illness or infection or concomitant drug or food. In addition, a statistically significantly higher rate of nervous system disorders were reported in the 400/200 mg group (91%) compared to the 400/100 mg dose group (67%). Notably, no significant differences were observed for moderate and severe treatment related nervous system AEs. Differences between the dose groups were observed for dizziness (15% vs 3%), anxiety (32% vs 22%) and somnolence (8% vs 0%). None of these differences were statistically significant. The majority of these events were mild and not considered related to study medication by the investigator.

As stated previously, the majority of the AEs reported were related to GI disorders. These events were mild to moderate in severity and approximately half were probably or possibly related to LPV/RTV. Five subjects in the 400/100 mg group and nine subjects in the 400/200 mg group reported severe GI events. Seven subjects developed severe diarrhea and "GGT increased", "LFT abnormal" and two subjects each reported nausea and vomiting. Four subjects prematurely discontinued study for these events.

In summary, the majority of the AEs reported in study M97-765 were mild to moderate in severity and not related to study medication. The AE profile observed in this trial is consistent with previous studies in PI-experienced trials. No new or unexpected AEs were observed following 144 weeks of dosing.

Most Common Adverse Events of at Least Moderate Severity and of Probable, Possible, or Unknown Relationship to LPV/RTV (Reported by >2% of All Subjects)

	Study M97-765		Study M97-720
Body System/ Adverse Event COSTART	**400/100 mg (n=36)**	**400/200 mg (n=34)**	**All dose groups (N=100)**
Body as a Whole			
Abdomen enlarged	0 (0%)	1 (3%)	4 (4%)
Abdominal pain	0 (0%)	2 (6%)	10 (10%)
Asthenia	2 (6%)	3 (9%)	9 (9%)
Fever	0 (0%)	0 (0%)	2 (2%)
Headache	1 (3%)	0 (0%)	7 (7%)
Pain	2 (6%)	1 (3%)	3 (3%)
Cardiovascular			
Hypertension	1 (3%)	1 (3%)	2 (2%)
Digestive			
Abnormal stools	1 (3%)	2 (6%)	8 (8%)
Diarrhea	11 (31%)	10 (29%)	27 (27%)
Dyspepsia	1 (3%)	0 (0%)	5 (5%)
Flatulence	0 (0%)	0 (0%)	4 (4%)
GGT increased	0 (0%)	2 (6%)	3 (3%)
Gastrointestinal disorder[a]	1 (3%)	1 (3%)	0 (0%)
LFT abnormal	1 (3%)	2 (6%)	2 (2%)
Nausea	1 (3%)	3 (9%)	16 (16%)
Vomiting	1 (3%)	0 (0%)	6 (6%)
Metabolic/Nutritional Disorders			
Hypercholesterolemia	3 (8%)	7 (21%)	13 (13%)
Hyperlipemia	2 (6%)	7 (21%)	12 (12%)
Obesity	0 (0%)	2 (6%)	0 (0%)
SGPT increased	0 (0%)	2 (6%)	3 (3%)
SGOT increased	1 (3%)	0 (0%)	4 (4%)
Weight loss	0 (0%)	4 (12%)	2 (2%)
Musculoskeletal			
Myalgia	2 (6%)	0 (0%)	2 (2%)
Nervous			
Depression	2 (6%)	0 (0%)	0(0%)
Insomnia	0 (0%)	2 (2%)	3 (3%)
Paresthesia	1(3%)	1 (3%)	2 (2%)
Libido decreased	0 (0%)	0 (0%)	2 (2%)
Respiratory			
Bronchitis	0 (0%)	0 (0%)	2 (2%)
Skin/Appendages			
Rash	2 (6%)	0 (0%)	4 (4%)
Urogenital			
Breast enlargement#	0 (0%)	1 (3%)	0 (0%)
Hematuria	2 (6%)	0 (0%)	0 (0%)
Hypogonadism#	0 (0%)	0 (0%)	2 (2%)
Metrorrhagia	0 (0%)	0 (0%)	1 (1%)

NOTE: Mild adverse events and events considered probably not or not related to LPV/RTV were excluded.

[a] Each case of treatment-related gastrointestinal disorder was associated with gastroesophageal reflux disease.

Percentages are based on the total number of male or female subjects in each dose group.

Cross Reference: Statistical Table 14.3.1__2.1 and Appendix 16.2__7.1.

Adverse Events of Interest

In the original and subsequent NDA reviews events of hepatitis and pancreatitis along with metabolic complications, specifically new onset diabetes and fat redistribution were evaluated in detail. For this review these events were reviewed to determine if changes to the package insert were warranted.

Hepatitis

In studies M97-720 and M97-765 four cases of hepatitis were reported. In study M97-720 one subject was diagnosed with acute hepatitis A. The other subject experienced severe hepatitis on study day 1275. His ALT and AST values were 258 U/L and 68 U/L, respectively. Additional details on this case were not provided. Study medications were interrupted on day 1282 and resumed on day 1317. The subject remains on study without further complications.

In study M97-765 one subject reported clay colored stools and dark urine in conjunction with elevated AST and ALT values. The investigator attributed this event to NVP. All study medications were interrupted on days 85-93 and then resumed, with the exception of NVP. Study medications were prematurely discontinued on day 253 due to diarrhea. At that time the AST and ALT values were 74 and 131 respectively. Another subject with HCV infection experienced end-stage liver disease. This subject remained on study medication and completed the trial. Of note, this subject did not develop grade 3-4 elevations in transaminases during the study.

The package insert contains a PRECAUTION regarding hepatic impairment and toxicity. Further revisions to the label are not needed at this time.

Pancreatitis

Two cases of pancreatitis were reported in study M97-765. In both cases alternative etiologies were given, specifically treatment with ddI, an NRTI known to cause pancreatitis. In one subject pancreatitis was reported after 5 months of treatment with LPV/RTV. The investigator felt the event was possibly due to LPV/RTV, NVP or ddI. Study drug was interrupted and ddI was replaced by 3TC. The event resolved after 39 days and the subject completed the study. The second subject developed pancreatitis after 1 ½ years of treatment. All study medications were interrupted for approximately 2 weeks until resolution of the event. DDI and D4T were replaced with ZDV and ABC. The subject completed the study without further complications. Of note, this subject developed grade 4 increases in triglycerides (1781 mg/dL) on study day 679; however, the event of pancreatitis resolved (day 603) before the grade 4 increase in triglyceride was observed. His screening triglyceride value was 733 mg/dL. The triglyceride values between Weeks 36 and 96 ranged from 296-869 mg/dL.

No new cases of pancreatitis between Weeks 72 and 204 were reported. This finding is encouraging given the concern that subjects who develop triglyceride values > 1000 mg/dL, a known laboratory abnormality for the ritonavir component of this product, may be at increased risk for pancreatitis. In the original NDA, we noted that subjects with a history of pancreatitis might be at increased risk for recurrence during lopinavir/ritonavir treatment; therefore, evaluation of pancreatitis during planned and ongoing studies and post-marketing is still essential.

The package insert contains a WARNING regarding the development of pancreatitis, including those who developed marked triglyceride elevations. Based on the two cases described above, no revisions are needed at this time to the WARNING section.

New onset diabetes

One case of new onset diabetes was reported in study M97-720.This subject had a family history of diabetes. Elevated glucose was observed on study day 679. The subject continued in the study and the diabetes was controlled with diet.

New onset diabetes/hyperglycemia is a PI class warning. No changes to this section are warranted at this time.

Fat redistribution

Fat redistribution, including central obesity, dorsocervical fat enlargement, peripheral and facial wasting, breast enlargement and "cushingoid" appearance, has been observed in subjects receiving ARV therapy. No uniform definition exists for fat redistribution and the diagnosis of fat redistribution is based on subjective clinician or subject assessment. As a result, objective assessment of this AE is difficult. Abbott pooled the terms obesity, lipodystrophy, Cushings syndrome, enlarged abdomen, and breast enlargement to assess this syndrome.

In antiretroviral-naïve subjects (study M97-720), AEs of body fat composition changes were observed in 25 subjects. All but three of the events occurred after 9 months of treatment. The majority of cases were related to peripheral and facial wasting. Few subjects developed central obesity. Most subjects remained on study medications. Three subjects discontinued d4T/3TC and three additional subjects discontinued d4T. D4T is known to cause lipoatrophy.

In treatment-experienced subjects (study M97-765), AEs relating to fat redistribution were observed in 17 subjects. All but four of the events occurred after approximately one year of treatment with LPV/RTV. Similar to study M97-720, the majority of cases were related to peripheral and facial wasting. Ten subjects developed an increase in abdominal girth. No subjects prematurely discontinued treatment for these events.

Fat redistribution is a well recognized AE related to antiretroviral treatment. No changes to the package insert regarding fat redistribution are warranted at this time.

Skin Reactions:

M97-720: Treatment-related rash was reported in 18 subjects. Fourteen subjects developed a mild rash and four subjects developed a moderate rash. The events were described as macular and papular in nature. No cases of severe rash were reported. One subject temporarily interrupted study medication due to rash and three subjects received concomitant medications to treat the rash. The median time to onset was 20 days (1-1090) and the median duration was 37 days (1-210).

M97-765: Treatment related rash was reported in 12 subjects; five subjects in the 400/100 mg group and seven subjects in the 400/200 mg group. Of the 12 subjects who developed a rash, 11 were mild and one moderate in severity. For nine subjects, the investigator also attributed the rash to NVP. One subject permanently discontinued study due to rash. In this case the investigator attributed the rash to both LPV/RTV and NVP. This subject developed a mild rash on days 4-10 during dosing with LPV/RTV and Combivir, and then subsequently developed a moderate rash after 33 days of dosing with LPV/RTV and six days of dosing with NVP. LPV/RTV and NVP were interrupted prior to the moderate rash due to elevated ALT. Four subjects received concomitant medications to treat the rash. The median time to onset was 20 days (4-1098) and the median duration was 12 days (4-413).

In addition, one case of exfoliative dermatitis/skin peeling was reported on study day 57. The event lasted for 15 days. The investigator attributed the event to "contact with nail polish". No action was taken and all study medications including LPV/RTV and NVP were continued. Based on the narrative of this case and the fact all study medications were continued without interruption, I agree with the assessment that the event was non-serious and most likely not related to study treatment.

As stated previously, serious skin reactions including SJS were reported in the Early Access Program and the LPV/RTV once daily versus twice daily clinical trial. As a result we consulted the Office of Drug Safety to conduct a search of the AERS database for serious skin reactions. The ODS consult is summarized below. Refer to Appendix B for the consult and full description of the cases.

Fourteen unduplicated postmarketing reports of serious skin reactions were reported to the Adverse Event Reporting System (AERS) between September 2000 and April 2004. Some of the cases were observed in the Early Access Program and reported to the IND and AERS. The serious skin reactions included Stevens Johnson syndrome (5), erythema multiforme (4), porphyria cutanea tarda (2), TEN (1), vesiculobullous rash (1), and severe blister (1). I agree with the ODS assessment that the majority of these cases are confounded by concomitant medications; however, one cannot rule out the contribution of LPV/RTV.

Five cases of SJS were reported to AERS, of which four are confounded by concomitant medications that are associated with SJS, including voriconazole, moxifloxacin, ciprofloxacin and nevirapine. SJS is listed in the package insert for each of these drugs. The remaining subject received LPV/RTV, indinavir, ddI and d4t. After two weeks of treatment the subject developed fevers, dyspnea, and desquamated skin of the ear lobes, trunk and face with ulcers of the mouth, anal region and urethra. Blood cultures were positive for klebsiella pneumonia and E. coli. The subject subsequently died of suspected agranulocytosis, septic shock, SJS and acute pancreatitis.

Two of the four cases of erythema multiforme, were confounded by concomitant medications. Both received abacavir and one was diagnosed with a suspected abacavir hypersensitivity reaction and the other was suspected as a drug interaction between LPV/RTV and phenytoin. The remaining two cases appear related to LPV/RTV treatment. Both subjects were not receiving any medications known to cause erythema multiforme. In both cases the subjects recovered after discontinuation of LPV/RTV and one subject had a "prompt" reoccurrence of the rash following LPV/RTV rechallenge.

Interestingly, two cases of porphyria cutanea tarda (PCT) were reported. PCT was reported in one subject after one month of LPV/RTV and Combivir treatment. The subject was hospitalized with PCT with lesions mostly on the upper extremities. LPV/RTV was discontinued and the event resolved. Treatment with Combivir continued. The second case occurred after 6 weeks of treatment with LPV/RTV, EFV, abacavir and indinavir. The patient developed multiple blisters on his hands. PCT was diagnosed based on skin biopsy. The blister showed immediate improvement when all ARVs were discontinued. Both subjects' condition improved when LPV/RTV was discontinued and neither subject had any risk factors for PCT.

In summary, cases of serious or severe skin reactions were only reported in treatment-experienced subjects and most were confounded by concomitant medications known to cause these particular reactions. Although the contribution of LPV/RTV to these cases is unknown, the possibility exists that the events were unrelated to LPV/RTV use. A few cases were reported with no alternative etiologies; therefore the Adverse Reaction, Postmarketing subsection of the package insert was revised to state that cases of SJS and EM were reported during LPV/RTV administration.

C.2. Deaths and Non-Fatal Serious Adverse Events

Deaths:

One death occurred in study M97-720. The subject died during study Week 149, one day after the last dose of study medication due to an unknown cause. At Week 146 the subject was found to have a spinal cord mass on CT. Surgery was performed and was subsequently complicated by a perioperative MI. Left coronary artery blockage, 40% blockage of the left circumflex and left ventricular systolic dysfunction were present. The nonfasting lipid values during treatment included maximum cholesterol of 245 mg/dL at Week 60 and a maximum triglyceride of 571 mg/dL at Week 120. Empiric therapy for extrapulmonary TB was started and the subject was

discharged nine days after the surgery. The subject was described as having "passed out" at home and died one day after discharge. Both the investigator and Abbott considered the death possibly related to study drug, although the alternative etiology of cardiac arrhythmia was provided.

Two deaths occurred in study M97-765. Both deaths occurred during the first 72 weeks of treatment and were reviewed in the original NDA. A summary of the deaths is provided below.

Subject 417 was hospitalized after approximately 7 months of LPV/RTV treatment for pneumonia. During this hospitalization, LPV/RTV treatment was interrupted. On admission the subject had elevated AST (558 U/L rose to 822 U/L), ALT (113 U/L), and LDH (2635 U/L). Bilirubin levels were normal. The subject also had acute renal failure with a creatinine of 2.2 mg/dL which rose to 11.5 mg/dL two days later. CPK on admission was 22,000 U/L. Rhabdomyolysis was suspected. Transaminase levels returned to normal; however, acute renal failure progressed with creatinine rising to 24.3 mg/dL seven days after admission. The subject died approximately eight days after admission due to progressive renal failure. The investigator considered the events pneumonia and rhabdomyolysis as probably not related to study drug; however, Abbott considered these events possibly related given the lack of a clinically verifiable alternative etiology. Further complicating this case, the subject was hospitalized at month two of study for PML.

The second death was due to metastatic lung cancer diagnosed nine weeks after study in a subject with a heavy smoking history. This event was not related to study medication.

SAEs:

Please refer to the appendix for a complete list of SAEs.

In study M97-720, 26 subjects experienced one or more SAEs through Week 204. SAEs reported by two subjects included abdominal pain, abscess, constipation, nausea, vomiting, dyspnea, pneumonia and pneumothorax due to gun shot wounds. Infection was the only SAE experienced in 3 or more subjects. SAEs considered possibly or probably related to LPV/RTV by the investigator were reported in 3 subjects. The SAEs included cardiac arrest, diarrhea and entercolitis with fever.

The case of cardiac arrest is summarized above.

One subject was hospitalized for entercolitis with microabscesses and granulomata approximately 11 weeks after initiating study treatment. Because the event was not linked definitively to an infectious agent via culture, the investigator considered the event possibly related to LPV/RTV. Of note, the subject experienced gastroenteritis during the lead-in period of the study, his baseline CD4 was < 100 and granulomata were seen on pathology. As a result, an inflammatory reaction resulting from immune reconstitution is a possible alternative etiology for this event.

Another subject was hospitalized for fever, sweating and asthenia attributed to disseminated MAI infection on study day 10. During hospitalization the subject experienced diarrhea (8-12 times per day). Study medication was interrupted and the subject was rechallenged two days later. The hospitalization was prolonged by the recurrence of diarrhea and dehydration upon re-initiation of study drug. The possibility exists these events were also related to MAI infection.

In study M97-765, 17 subjects developed an SAE through Week 144. In addition, two SAEs occurred prior to study drug initiation. More subjects (n=11) in the 400/200 group developed a SAE compared to the 400/100 mg group (n=6). Of note, in the original NDA review, SAEs were reported in 13 subjects through Week 72. Overall, the majority of events were considered unrelated to LPV/RTV. SAEs judged by the investigator as possibly or probably related to LPV/RTV occurred in three subjects in the 400/100 mg group and two subjects in the 400/200 mg

group. Events considered possibly or probably related included bone necrosis, cerebrovascular accident, cholecystitis, diarrhea and lung edema.

The bone necrosis event occurred in a male subject who received LPV/RTV 400/100 mg. The subject complained of persistent left hip pain for six months prior to surgery. The subject required outpatient surgery for the event on Study Day 760. Study medication continued through Week 204. Cases of avascular necrosis were reported previously in the literature and from retrospective studies and are considered a consequence of HIV infection and/or ARV therapy, particularly PIs.

The event of cerebral infarct occurred in a 58 year old male who received LPV/RTV 400/200 mg. His past medical history is remarkable for hypercholesteremia, hypertension and a strong family history of cardiovascular disease including MI, CHF, hypertension and CVA. The cerebral infarct occurred on study day 1081. The etiology of his CVA was embolic and surgery was not considered an option. He was placed on enoxaparin and subsequently warfarin. Study medications were not interrupted and the subject completed the trial. The possibility exists this event was either related to LPV/RTV or history of elevated lipid levels and strong family history.

The case of cholecystitis occurred in a 47 year old male approximately 5 months after initiating study treatment in the 400/200 mg group. The subject had a past history of multiple gastrointestinal conditions and a 2-year history of intermittent right upper quadrant pain. A cholecystectomy was performed and the subject recovered without interruption of study medication.

A 42 year old male was hospitalized for appendicitis and subsequent life-threatening pulmonary edema after approximately seven months of LPV/RTV treatment. The pulmonary edema resolved after three days. The investigator suggested this event was a result of a possible reaction with fentanyl. Of note the subject did not receive study medications for over 48 hours prior to the event and the clinical course was suggestive of a chemical pneumonitis triggered by possible perioperative aspiration.

A 37 year old male who received LPV/RTV 400/100 mg was hospitalized for severe diarrhea with abdominal cramping after three weeks of treatment. The subject has a history of prolonged periods of diarrhea and was hospitalized in the past for diarrhea. Study medication was interrupted for six days and the event resolved.

The remaining events were considered probably not or not related to LPV/RTV. For several of the events, subjects had a previous medical history, family history or received concomitant medications known to be associated with the event. One subject in each dose group prematurely discontinued study for an SAE related to MI on Study Day 1 and suicide attempt on Study Day 1093. Both events were not considered related to study medication.

C.3. Discontinuations due to Adverse Events

The AEs leading to premature discontinuation in studies M97-720 and M97-765 are listed in the table below. Nine subjects in each study prematurely discontinued due to an AE. No new or unexpected AEs leading to premature study discontinuation were observed.

In study M97-720 nine subjects prematurely discontinued due to an AE. Six subjects prematurely discontinued for events probably or possibly related to LPV/RTV. These events were related to increases in cholesterol, ALT/AST, hepatomegaly and diarrhea. The events relating to liver toxicity are discussed in the AE of interest section below.

In study M97-765, nine subjects prematurely discontinued study due to AEs. Five subjects prematurely discontinued for events noted to be probably or possibly related to LPV/RTV by the investigator. AEs related to GI disorders contributed to premature discontinuation for 4 of the 5

subjects. One subject prematurely discontinued due to rash. Of note, the rash occurred after 33 days of dosing with LPV/RTV and after six days of dosing with nevirapine.

Adverse Events Leading to Premature Discontinuation

Dose Group	Subject	Adverse Event	Day of Onset	Relationship to LPV/RTV
Study M97-720				
200/100 mg	104	Elevated Glucose	539	Probably not – history of diabetes
	111	Hypercholesterolemia	1280	probable
	115	Arthalgia Depression Fatigue	738	Possible Probably not Probable
400/100 mg	116	Diarrhea	571	Probable
	211	Lymphoma-like reaction	22	Not related – secondary to immune suppression
	238	Increased ALT/AST	995	Probable – coexisting HCV
400/200	210	Alcohol intolerance	411	Not related – history of alcoholism
	240	Increased ALT/AST	521	Possible
	274	Hepatomegaly with liver fatty deposits and tenderness	809	Probable
Study M97-765				
400/100 mg	316	Depression	728	Probably not
	356	MI	1	Not related
	405	Diarrhea	501	Probable
	411	Flatulence Diarrhea Nausea Vomiting	1	Probable
	466	Rash	33	Probable
400/200 mg	309	Suicide attempt	1093	Not related
	318	Diarrhea	168	Probable
	323*	LFT increased	613	Not related
	413	Asthenia (moderate) Asthenia (mild) diarrhea	515 651 532	Possible Probably not Possible

*Subject was prematurely discontinued for a non-treatment emergent AE

C4. Clinical Laboratory Findings

Hematology

Overall, no clinically significant hematology abnormalities were observed in studies M97-720 and M97-765. Summarized below are the findings from each trial.

In study M97-720, no clinically significant mean changes from baseline in hematology parameters were observed through Week 204. Eight subjects developed AEs associated with abnormal hematology values. Six cases of neutropenia and two cases of anemia were reported. Regarding the neutropenia AEs, one case was related to laboratory error, two were preceded by an upper respiratory viral infection and the remaining two subjects only had mild decreases in neutrophil counts. The last two subjects were receiving chemotherapy or long-term sulfamethoxazole. The investigator considered the anemia AEs as related to concurrent medical conditions or medication.

In study M97-765, no clinically significant mean changes from baseline in hematology variables were observed at Week 144. One subject experienced a grade 3/4 decrease in neutrophil counts on days 28 and 34. Throughout the trial the neutrophil values fluctuated within normal limits to $< 0.75 \times 10^9$/L. No grade 3/4 increases in hematology values were reported in the study. Four subjects experienced AEs associated with abnormal hematology values. All four subjects completed the trial. Leukopenia was

reported for one subject and increased absolute neutrophil count and WBC was reported for another subject. Two subjects were hospitalized due to anemia. In one case the investigator attributed the anemia to ZDV and subsequently replaced ZDV with ddI. The other case of anemia was secondary to GI bleeding in a subject receiving NSAID and ribavirin treatment.

Clinical Chemistries

The FDA analysis primarily focused on the incidence of grade 3 and grade 4 laboratory abnormalities and mean change from baseline for selected laboratory tests. These findings are described in the table below. Overall, the types of laboratory abnormalities observed in studies M97-720 and M97-765 are consistent with those observed in other LPV/RTV trials. The incidences of the laboratory abnormalities observed in these trials are slightly higher than those observed over 48 weeks in studies 863 and 888. Differences are most likely attributed to duration (48 weeks vs 144-204 weeks) and sample size. Of note, blood samples for clinical chemistries were collected without regard to fasting. No new or unexpected laboratory abnormalities were observed following 144 – 204 weeks of treatment.

In study M97-765, a larger proportion of subjects in the 400 mg/200 mg dose group developed grade 3+ laboratory abnormalities compared with the 400 mg/100 mg dose group. No statistically significant differences were detected between the LPV/RTV dose groups for the proportions of subjects developing grade 3+ abnormalities.

Proportion (%) of Subjects with Grade 3 or 4 Laboratory Abnormalities*

Chemistry Variable	Study M97-765 144 Weeks		Study M97-720 204 Weeks
	400 mg/100 mg (N=36)	400 mg/200 mg (N=33**)	All subjects (N=100)
Glucose (>250 mg/dL)	1 (3%)	2 (6%)	4 (4%)
Creatinine (>3 x ULN)	0 (0%)	1 (3%)	0 (0%)
Uric Acid (>12 mg/dL)	0 (0%)	1 (3%)	3 (3%)
SGOT/AST (>5 x ULN)	2 (6%)	6 (18%)	9 (9%)
SGPT/ALT (>5 x ULN)	3 (8%)	8 (24%)	9 (9%)
GGT (>5 x ULN)	8 (22%)	12 (36%)	6 (6%)
Total cholesterol (>300 mg/dL)	11 (31%)	14 (42%)	22 (22%)
Total bilirubin > 3.48 mg/dL	1 (3%)	0 (0%)	1 (1%)
Triglycerides (>750 mg/dL)	8 (22%)	14 (42%)	22 (22%)
Neutrophils (< 0.75 x 10^9/L)	0 (0%)	0 (0%)	5 (5%)
Amylase (>2 x ULN)	2 (6%)	2 (6%)	4 (4%)

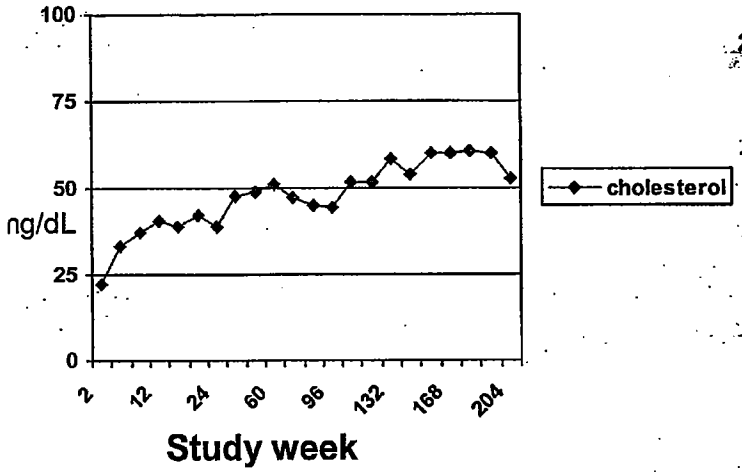
* This table includes all subjects with any chemistry value meeting very high criteria and above baseline.

** One of the 34 subjects receiving 400 mg/200 mg did not have a post-baseline chemistry value and is excluded from all chemistry analyses.

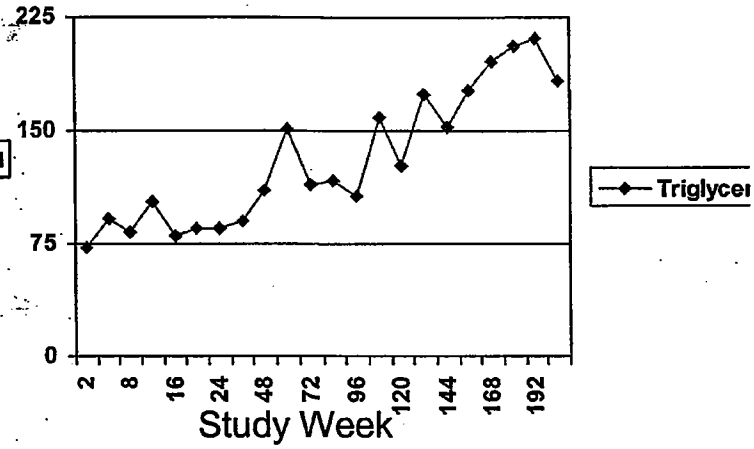
Lipids:

The mean change from baseline for cholesterol and triglycerides are displayed in the figures below. In study M97-720 the mean change from baseline at Week 204 for cholesterol and triglycerides was 159 mg/dL and 154 mg/dL, respectively. Overall cholesterol and triglyceride values increased over time. In study M97-765 greater increases in mean total cholesterol and triglycerides were observed for the 400/200 mg group compared to the 400/100 mg group throughout the study. Similar to study M97-720, cholesterol values increased over 120 weeks of treatment and then decreased slightly from Weeks 120-144. Significant variability in the triglyceride values were seen over time. As noted previously, blood samples for clinical chemistries were collected without regard to fasting.

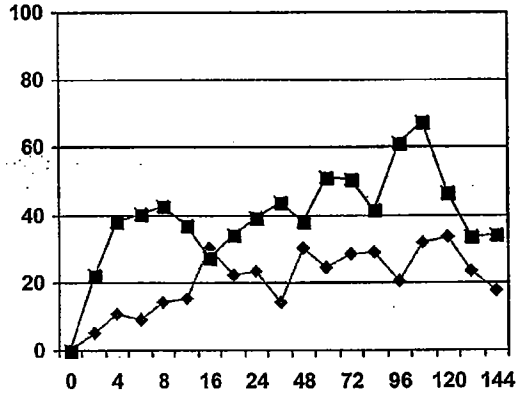
Study M97-720
Mean Change from Baseline
Over Time for Cholesterol



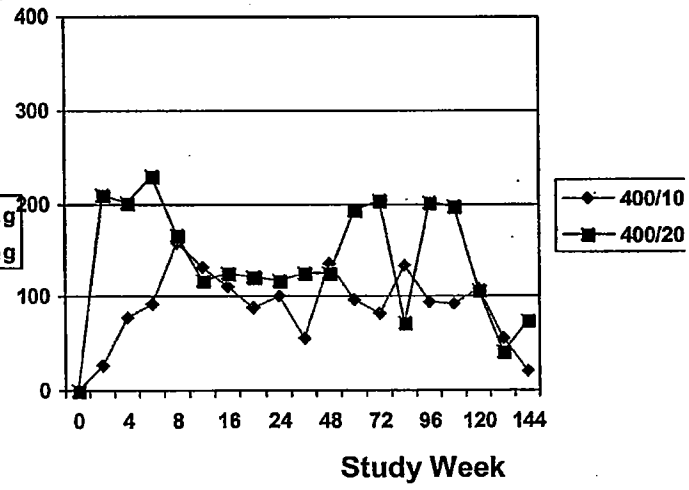
Study M97-720
Mean Change from Baseline
Over Time for Triglycerides



Study M97-765
Mean Change from Baseline
Over Time for Cholesterol



Study M97-765:
Mean Change from Baseline
Over time for Triglycerides



A substantial proportion of subjects developed lipid abnormalities. In study M97-720, thirty-four subjects (34%) developed a grade 3/4 lipid abnormality. Of the 34 subjects, 12 each had elevated cholesterol,12 had elevated triglycerides, and 10 had both elevated cholesterol and triglycerides. One subject discontinued study drug on day 1280 due to hypercholesterolemia. Hyperlipidemia and/or hypercholesterolemia were reported as an AE in 30 subjects. Antihyperlipidemic agents were used by 20 subjects.

In study M97-765, 32 (45%) subjects developed a lipid abnormality. Of the 32 subjects, 10 had elevated cholesterol, 7 had elevated triglycerides and 15 had both elevated cholesterol and triglycerides. Six subjects developed a grade 3+ lipid elevation after Week 48. No subjects prematurely discontinued study for a lipid abnormality. A total of 18 subjects initiated treatment with an antihyperlipidemic agent. Notably, at the final study visit, 15% of subjects in the 400/200 mg group had grade 3+ cholesterol compared to no subjects in the 400/100 mg group.

For study M97-765, Abbott conducted several analyses to evaluate the risk of developing grade 3/4 elevations in cholesterol or triglycerides. Antiretroviral-experienced subjects with baseline cholesterol > 200 mg/dL were at increased risk for developing grade 3+ cholesterol elevations (risk ratio = 4.25 95% CI 2.16, 8.35). A similar finding was observed for triglycerides. Subjects with baseline triglycerides > 400 mg/dL were at increased risk for grade 3+ elevations in triglycerides (risk ratio = 2.86; 95% CI 1.60-5.11). We also evaluated the risk of developing grade 3+ elevations in triglycerides in subjects with baseline triglycerides $\geq$ 250 mg/dL. The risk ratio for developing grade 3+ triglyceride elevations in triglycerides was approximately 4 for subjects with baseline triglyceride values $\geq$ 250 mg/dL.

We also conducted similar analyses for study M97-720. Treatment-naïve subjects with baseline cholesterol $\geq$ 200 mg/dL or triglycerides $\geq$ 250 mg/dL were at increased risk for developing grade 3+ cholesterol or triglyceride elevations. The risk ratio was approximately 2.6 for cholesterol and 5 for triglycerides. No subjects with elevated triglycerides (>1000 mg/dL) developed concomitant pancreatitis.

Transaminases:

Overall, 13 subjects in study M97-765 and 11 subjects in study M97-720 developed grade 3/4 increases in transaminases. These findings are consistent with previous studies in antiretroviral-experienced and naïve subjects. Two subjects in study M97-720 and one subject in study M97-765 prematurely discontinued study due to elevated transaminase values. The two subjects in study M97-720 were co-infected with either HBV or HCV. The remaining subject in study M97-765 was prematurely discontinued due to elevated transaminase values attributed to concomitant treatment with oxandrin; however, this subject had elevated values prior to treatment with oxandrin.

In study M97-765, Abbott noted subjects in the 400 mg/200 mg dose group demonstrated a trend towards a higher rate of grade 3/4 AST and ALT elevations compared to subjects in the 400 mg/100 mg dose group (AST: 18.2% versus 5.6% [p=0.140]; ALT: 24.2% versus 8.3% [p=0.102]). Of note, subjects in this study were also receiving NVP, which is also known to cause increases in AST and ALT. No subjects prematurely discontinued study for an LFT abnormality.

Interestingly, only 3 subjects each in study M97-765 and M97-720 had a new onset of a grade 3+ ALT or AST increase occurring after the first year of treatment. Overall 9/24 subjects developed first time elevations after Week 24. These data suggest increased incidences of transaminase abnormalities are not observed with increased duration of treatment.

In study M97-720, transaminase elevations returned to within normal range or baseline levels in 6/11 subjects while therapy was continued or after rechallenge. Similarly, transaminase elevations in study M97-765 returned to within normal range or baseline levels in 9/13 subjects following treatment interruption or continued therapy.

For studies M97-720 and M97-765 we conducted additional analyses to evaluate concurrent grade 3-4 elevations in ALT and total bilirubin. In study M97-720, one subject had a concurrent grade 4 ALT and bilirubin; however, the laboratory abnormalities were due to acute hepatitis A infection. No subjects in study M97-765 developed concurrent grade 3/4 elevations in ALT and total bilirubin.

Co-infected Subjects:

In sNDA 003, Abbott reported that subjects with baseline hepatitis B or C were found to be at a significantly increased risk of developing grade 3/ 4 transaminase elevations in both the lopinavir/ritonavir group (risk ratio = 3.49; 95% CI 1.30, 9.38) and the nelfinavir group (risk ratio = 10.16; 95% CI 3.76, 27.47). In study M97-720, five of the 11 subjects with HBV and/or HCV experienced grade 3 -4 elevations in ALT compared to 6/89 subjects who had negative baseline serologies for HBsAG or HCV Ab. Similar to earlier findings, antiretroviral-naïve subjects with positive baseline serologies for viral hepatitis were at increased risk for grade 3-4 increases in transaminases (relative risk = 6.74; 95% CI 2.46-18.48).

In study M97-765, 10 subjects were co-infected with HBV or HCV. Of the ten subjects two had grade 3/4 increases in AST and/or ALT compared to 10/59 subjects who were negative for HBV or HCV.

The package insert includes a PRECAUTION regarding subjects 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. Based on the findings in study M97-720 and M97-765 revisions to the PRECAUTION section are not warranted. The package insert includes adequate cautionary statements for potential hepatic toxicity.

Glucose

In study M97-720, four subjects developed grade 3+ glucose elevations (>250 mg/dL). Three of these subjects had risk factors for diabetes; two had preexisting diabetes and one had a family history. One subject prematurely discontinued study due to hyperglycemia. Two subjects were treated with oral hypoglycemics and continued treatment with LPV/RTV.

Similarly, in study M97-765, three subjects developed grade 3+ elevations in glucose; of which two had pre-existing diabetes. In the two subjects with pre-existing diabetes, the glucose values decreased to near or below baseline value with continued LPV/RTV treatment. One subject continued insulin treatment without dose adjustments and another subject initiated oral hypoglycemics for treatment of hyperglycemia.

No new findings regarding elevations in glucose were observed. New onset diabetes, exacerbation of preexisting diabetes and hyperglycemia is a known potential AE in subjects receiving protease inhibitor therapy. A warning regarding these events is included in all protease inhibitor package inserts. Revisions to this WARNING based on the information from studies M97-720 or M97-765 are not warranted at this time.

ECG Findings:

In studies M97-720 and M97-765 analyses of mean change from baseline were performed for the ECG values of PR, QT, QTcB, and QTcF intervals. Of note, no specific or standardized instructions were provided to investigators regarding measurement of electrocardiographic intervals. The results of these findings are presented below.

QTc

In the original NDA, we concluded that although the mean and median change from baseline for the QTc interval increased over time, the clinical significance of these findings appears minimal. In addition, an indication of a dose response relationship for LPV/RTV was not apparent. Although the EKGs were not

obtained at Cmax, data did exist at higher doses (concentrations) than the approved regimen of 400/100 mg bid. These data suggest higher concentrations do not increase the risk of QTc prolongation.

The information presented in the 204 week study report for M97-720 did not contradict the above findings nor contribute to additional findings. The ECG analyses were based on the mean change from the final available value. Due to the protocol-defined timing of ECG determinations and because many subjects continued on treatment in the study, the final available value for most subjects occurred at Week 2, 4 or 8. The magnitudes of the mean increases in QTcB and QTcF were minimal and not statistically significant. The mean change from baseline to final evaluation for QTcB and QTcF intervals were 1.57 and 2.11, respectively. Eight subjects had QTc values > 450 msec; of which four had baseline values > 450. No adverse events were reported with these ECG abnormalities. The incidence of QTc values > 450 in this study appears to be driven by anomalies at a single study site. Abbott reviewed data between this site and from other sites and determined the discrepancies were related to abnormally high heart rates.

In study M97-765, no statistically significant mean changes from baseline for QT, QTcB, and QTcF intervals were observed at any visit, and no statistically significant differences between dose groups were observed. A summary of the data is presented in the table below. Four subjects had QTc values > 450, of which one had a baseline value of 452. One subject had a cardiovascular related AE (see discussion under PR interval findings).

Overall these data do not alter the original findings, specifically; treatment with LPV/RTV does not lead to clinically significant QTc prolongation.

	Study M97-765			
Interval Study Evaluation (Week)	**Dose Group/Study**	**N**	**Baseline Mean**	**Mean Change from Baseline (SE)**
QTcB Interval				
Week 2	400 mg/100 mg	34	401.1	4.0 (2.2)
	400 mg/200 mg	31	409.6	1.0 (2.3)
Week 4	400 mg/100 mg	32	402.5	2.7 (2.9)
	400 mg/200 mg	28	411.0	-2.6 (3.1)
Week 48	400 mg/100 mg	28	401.4	2.3 (3.0)
	400 mg/200 mg	23	410.1	-0.4 (3.4)
Final study evaluation	400 mg/100 mg	36	403.2	4.6 (3.6)
	400 mg/200 mg	33	409.2	2.8 (3.8)
QTcF Interval				
Week 2	400 mg/100 mg	34	389.2	3.8 (2.1)
	400 mg/200 mg	31	394.9	1.7 (2.2)
Week 4	400 mg/100 mg	32	391.9	1.8 (2.6)
	400 mg/200 mg	28	396.4	-2.1 (2.8)
Week 48	400 mg/100 mg	28	390.4	2.3 (2.9)
	400 mg/200 mg	23	394.2	0.8 (3.2)
Final study evaluation	400 mg/100 mg	36	391.8	4.8 (3.6)
	400 mg/200 mg	33	395.0	2.2 (3.8)

PR:

In the original NDA a statistically significant increase in PR interval in subjects who received LPV/RTV compared to NLV was observed. The changes were not considered clinically significant. Nine LPV/RTV-treated subjects had PR interval $\geq$ 210 msec, of which 3 had a baseline PR interval > 210 msec. All subjects continued on study drug without AEs.

Similar findings were observed in studies M97-720 and M97-765. In study M97-720, a statistically significant increase in PR interval (5 msec) was observed for all subjects. In comparison a statistically significant increase from baseline was observed in study M97-765 for the 400/200 mg group at Week 2 only and at Week 4 for the 400/100 mg group. Two subjects in each study had PR intervals > 210 msec during study.

In study M97-765 one subject had a PR interval at Week 2, 4, 48 and end of study of 212, 208, 172 and 170 msec, respectively. Borderline first degree AV block was reported at Week 2 and 4; however the investigator determined this was not clinically significant. A clinically significant ECG finding for Subject No. 424 (45-year-old male) on Day 1092 (last evaluation) was reported as "elongated QTc, possible first degree AV block"; the subject was referred to a cardiologist. The QTc and PR values for this subject on Day 1092 were 480 msec (QTcB: 493 msec, QTcF: 485 msec) and 286 msec, respectively. A mild 3/6 systolic murmur was reported as an adverse event for this subject from Days 517 to 1092. The investigator considered the murmur not related to LPV/RTV, but alternatively related to the subject's past history of cardiovascular disease. No additional events were observed in this study.

In study M97-720, one subject who experienced a PR interval > 210 (215 msec).. This event was accompanied by mild substernal chest pain and was considered possibly related to LPV/RTV or increased stress and stomach problems. Borderline first-degree AV block was reported as an AE for another subject. This subject had a PR interval of 206 msec.

Overall, these findings do not appear clinically significant. No cases of second or third degree AV block were observed.

VII. Dosing, Regimen, and Administration Issues

No new dosing issues were identified in the studies submitted. In study M97-720 all subjects received the approved dosing regimen of 400/100 mg bid between Weeks 48-72. Administration of LPV/RTV 200/100 or 400/200 mg bid did not adversely affect efficacy or safety in this trial. In study M97-765 subjects were randomized to 400/100 or 400/200 mg bid for 144 weeks. Treatment with 400/200 mg bid for 144 weeks appears generally well tolerated. With the exception of obesity and sweating, the incidence of AEs are similar between the dose groups. Numerically, a higher incidence in CNS events such as dizziness, anxiety and somnolence were observed in the 400/200 mg group In addition, a larger proportion of subjects in the 400 mg/200 mg dose group had Grade 3+ chemistry abnormalities compared with the 400 mg/100 mg dose group.

VIII. Use in Special Populations

A. Ethnicity/Race, Age and Gender

Abbott did not provide analyses for ethnicity/race, age or gender effects on safety or efficacy. In the two trials submitted, over 90% of subjects were male and the majority were Caucasian. Based on the limited number of subjects enrolled in these studies (M97-720 N=100; M97-765 n=70), too few subjects in ethnicity or gender categories were available to make definitive conclusions regarding race or gender differences. Abbott conducted adequate age, race and gender analyses for their two phase 3 studies (M98-863 and M98-888) and submitted analyses as part of a phase 4 commitment to evaluate the relative treatment response, safety and tolerability of LPV/RTV in Caucasians vs. Blacks. Additional analyses are not required at this time.

B. Evaluation of Pediatric Program

The pediatric Phase II/III clinical trial data through 48 weeks was reviewed in a previous supplement to NDA 21-251 (SE8-004) and conclusions from that study were incorporated into the product label. No new pediatric data was submitted with this efficacy supplement. Studies are ongoing evaluating LPV/RTV in children < 6 months of age.

IX. Conclusions and Recommendations

A. Conclusions Regarding Safety and Efficacy

The studies submitted in this supplement provide important long-term safety and efficacy data in treatment-naïve and treatment-experienced subjects. LPV/RTV 400/100 mg BID in combination with other antiretroviral agents provided effective treatment in antiretroviral-naïve and antiretroviral experienced subjects through Weeks 204 and 144, respectively.

The response rate (HIV RNA< 400 copies/mL) for antiretroviral-naïve subjects was 71% at Week 204. In the antiretroviral-experienced study (M97-765), response rates were similar for the two dose groups, 400/100 mg and 400/200 mg. Approximately 50% of subjects enrolled in this study achieved HIV RNA < 400 copies/mL at Week 144.

Review of the long-term safety data in treatment-naïve and treatment-experienced subjects identified no new LPV/RTV-related toxicities. GI events and hyperlipidemia were the most commonly reported toxicities. With the exception of lipids, laboratory abnormalities did not appear to increase over time. Overall, treatment with LPV/RTV was generally well-tolerated for 144-204 weeks. Although not new, additional cases of serious skin reactions were reported through the Adverse Event Reaction System (AERS), thus leading to the addition of Stevens Johnson Syndrome and erythema multiforme events to the Adverse Reaction section of the package insert.

B. Recommendation on Approvability

From a clinical perspective, the efficacy and safety data presented in this supplement support the long-term administration (144-204 weeks) of LPV/RTV in treatment-naïve and treatment-experienced subjects.

C. Review of Labeling

Several changes were made to the package insert. This section highlights the major changes.

CLINCIAL PHARMACOLOGY:

Information from a multiple dose study in HIV and HCV co-infected subjects with mild to moderate hepatic impairment were included. Specifically, the following text was included.

Multiple doses of KALETRA 400/100 mg bid to HIV and HCV co-infected subjects with mild to moderate hepatic impairment (n=12) resulted in a 30% increase in lopinavir AUC and 20% increase in Cmax compared to HIV-infected subjects with normal hepatic function (n=12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs 99.31%, respectively). Caution should be exercised when administering KALETRA to subjects with hepatic impairment.

INDICATIONS AND USAGE and Description of Clinical Studies:

These sections were updated to include long-term efficacy results from two uncontrolled dose-ranging studies. Specifically the Week 204 efficacy results from study M97-720 in antiretroviral-naïve subjects and the Week 144 results from study M97-765 in antiretroviral-experienced subjects were included as follows.

Through 204 weeks of treatment in study 720, the proportion of patients with HIV RNA <400 (<50) copies/mL was 71% (70%) [n=100], and the corresponding mean increase in CD4 cell count was 440 cells/mm^3. Twenty-eight patients (28%) discontinued the study, including 9 (9%) discontinuations due to adverse events and 1 (1%) death. Through 144 weeks of treatment in study 765, the proportion of patients with HIV RNA <400 (<50) copies/mL was 54% (50%) [n=70],

and the corresponding mean increase in CD4 cell count was 212 cells/mm^3. Twenty seven patients (39%) discontinued the study, including 9 (13%) discontinuations secondary to adverse events and 2 (3%) deaths

PRECAUTIONS:

- A statement regarding immune reconstitution syndrome was added.

Drug Interactions

- Table 9: Established and Other Potentially Significant Drug Interactions was updated to include information with tenofovir, fosamprenavir, voriconazole, tadalafil and vardenafil.

Carcinogenesis, Mutagenesis and Impairment of Fertility

- Results from the long-term carcinogenicity studies with KALETRA were included.

ADVERSE REACTIONS:

- Table 10 (AEs) and 11 (laboratory abnormalities) were updated to include the Week 204 data from study M97-720 and the Week 144 data from study M97-765.
- SJS and EM were added to the postmarketing experience section

Appendix A

Adverse Events – All Grades and Regardless of Severity

AE Term	Study M97-765		Study M97-720	
	400/100 mg (N=36)	400/200 mg (n=34)	400/100 mg (N=51)	All subjects (N=100)
Body as a Whole				
Abdomen enlarged	1 (3%)	3 (9%)	6 (12%)	10 (10%)
Abdominal pain	9 (25%)	9 (7%)	18 (35%)	35 (35%)
Accidental injury	7 (19%)	7 (21%)	15 (29%)	24 (24%)
Allergic reaction	2 (6%)	5 (15%)	5 (10%)	14 (14%)
Asthenia	12 (33%)	11(32%)	26 (51%)	51 (51%)
Back pain	5 (14%)	3 (9%)	8 (16%)	14 (14%)
Chest pain	3 (8%)	5 (15%)	7 (14%)	14 (14%)
Chills	2 (6%)	1 (3%)	6 (12%)	10 (10%)
Fever	10 (28%)	10 (29%)	15 (29%)	30 (30%)
Flu syndrome	11 (31%)	4(12%)	4 (8%)	17 (17%)
Headache	12 (33%)	17(50%)	13 (25%)	45 (45%)
Infection	18 (50%)	12(35%)	25 49%)	44 (44%)
Infection bacterial	2 (6)%	3 (9%)	5 (10%)	10 (10%)
Infection fungal	4 (11%)	4(12%)	2 (4%)	3 (3%)
Pain	14 (39%)	15 (44%)	20 (39%)	45 (45%)
Cardiovascular				
Hypertension	3 (9%)	3 (9%)	15 (15%)	5 (10%)
Digestive				
Abnormal stools	11(31%)	12(35%)	27 (53%)	54 (54%)
Anorexia	3 (8%)	4(12%)	9 (18%)	15 (15%)
Constipation	3 (8%)	6(18%)	3 (6%)	7 (7%)
Diarrhea	26(72%)	22(65%)	36 (71%)	64 (64%)
Dyspepsia	8 (22%)	3 (9%)	11 (22%)	22 (22%)
Flatulence	7 (19%)	5(15%)	8 (16%)	13 (13%)
Gastrointestinal disorder	4 (11%)	4(12%)	1 (2%)	5 (5%)
Nausea	16(44%)	15(44%)	24 (47%)	57 (57%)
Rectal disorder	4 (11%)	3 (9%)	4 (8%)	10 (10%)
Vomiting	12(33%)	9(27%)	13 (25%)	30 (30%)

Hemic/Lymphatic				
Lymphadenopathy	9 (25%)	9(24%)	18 (35%)	38 (38%)
Metabolic/Nutritional				
Edema	2 (6%)	5(15%)	4 (8%)	9 (9%)
Musculoskeletal				
Arthralgia	5 (14%)	3 (9%)	7 (14%)	14 (14%)
Myalgia	8 (22%)	7(21%)	6 (12%)	9 (9%)
Nervous				
Anxiety	8(22%)	11(32%)	4 (8%)	11(11%)
Depression	6(17%)	6(18%)	13 (25%)	31 (31%)
Dizziness	1 (3%)	5 (15)	7 (14%)	14 (14%)
Insomnia	10(28%)	7(21%)	11 (22%)	19 (19%)
Paresthesia	9(25%)	10(29%)	17 (33%)	30 (30%)
Peripheral neuritis	4(11%)	5(15%)	5 (10%)	13 (13%)
Respiratory				
Asthma	4(11%)	4(12%)	9 (18%)	12 (12%)
Bronchitis	3 (8%)	4(12%)	11 (22%)	16 (16%)
Cough increased	14(39%)	16(47%)	20 (39%)	35 (35%)
Dyspnea	3 (8%)	4(12%)	9 (18%)	16 (16^)
Lung disorder	2 (6%)	7(21%)	2 (4%)	3 (3%)
Pharyngitis	14(39%)	13(38%)	29 (57%)	58 (58%)
Rhinitis	13(36%)	18(53%)	19 (37%)	42 (42%)
Sinusitis	3 (8%)	6(18%)	8 (16%)	15 (15%)
Skin/Appendages				
Acne	3 (9%)	3 (%)	7 (14%)	14 (15%)
Dry skin	4(11%)	4(12%)	3 (6%)	10 (10%)
Fungal dermatitis	2 (6%)	3 (9%)	4 (8%)	11 (11%)
Maculopapular rash	4(11%)	4(12%)	6 (12%)	12 (12%)
Nail disorder	1 (3%)	5 (15%)	7 (14%)	10 (10%)
Pruritus	3 (8%)	3 (9%)	3 (6%)	10 (10%)
Rash	12(33%)	13(38%)	20 (39%)	40 (40%)
Skin benign neoplasm	5(14%)	2 (6%)	10 (20%)	18 (18%)
Skin disorder	9(25%)	7(21%)	11 (22%)	23 (23%)
Sweating	3 (8%)	10(29%)*	4 (8%)	18 (18%)
Special Senses				
Conjunctivitis	3 (8%)	6(18%)	8 (16%)	12 (12%)
Urogenital				
Abortion#	0 (0%)	0 (0%)	1 (33%)	1 (25%)
Breast enlargement#	0 (0%)	1 (20)	0 (0%)	0 (0%)
Dysuria	1 (3%)	6(18%)	3 (6%)	5 (5%)
Fibrocystic breast#	1(50%)	0 (0%)	0 (0%)	0 (0%)
Impotence#	0 (0%)	2 (7%)	7 (15%)	13 (14%)
Metrorrhagia#	0 (0%)	0 (0%)	1 (2%)	1 (25%)
Unintended pregnancy #	0 (0%)	0 (0%)	1(33%)	1 (25%)
Vaginitis#	0(0.0%)	1(20%)	1 (33%)	2 (50%)

#based on number of women or men

List of Subjects Experiencing Serious Adverse Events – Study 765

Dose Group	Subject No.	Serious Adverse Event COSTART term(s)	Day of Onset	Serious Category[a]	Relationship to ABT-378/ritonavir	
					Investigator	Sponsor
400 mg/ 100 mg	317	Ileitis[b]	-19	Hospitalized	Not related	Probably not
	322	Bone necrosis	760	MSI	Possible	Possible
	365	Myocardial infarct*	1	Hospitalized	Not related	Not related
	401	Abdominal syndrome acute[c]	205	Hospitalized, MSI	Not related	Probably not
		Lung edema	207	Prolonged Hosp, LT, MSI	Possibly	Probably not
	415	Asthma	151	MSI	Not related	Probably not
		Pneumonia	443	Hospitalized	Not related	Probably not
	423	Diarrhea	21	Hospitalized	Possibly	Possibly
	425	Anemia	650	Hospitalized, MSI	Not related	Probably not
		GI hemorrhage	650	Hospitalized	Not related	Probably not
400 mg/ 200 mg	304	Urination impaired	93	Hospitalized	Not related	Probably not
		Back pain	94	Prolonged Hosp	Not related	Probably not
		Pneumonia	109	Hospitalized	Not related	Probably not
		Cholecystitis	159	Hospitalized	Possibly	Possibly
		Abdomen enlarged Nausea Vomiting	172	Hospitalized	Not related	Probably not
		Intestinal obstruction	317	Hospitalized	Not related	Not related
		Ileus	363	Hospitalized	Not related	Probably not
		Abdomen enlarged Abdominal pain Nausea	610	Hospitalized	Probably not	Probably not
		Abdomen enlarged Anorexia Diarrhea Vomiting Nausea Abdominal pain Dyspnea	737	Hospitalized	Not related	Probably not
		Dehydration	739	Prolonged Hosp	Probably not	Probably not
		Abdomen enlarged Abdominal pain Dehydration Diarrhea Postural hypotension Nausea	765	Hospitalized	Probable	Probably not
		Intestinal Obstruction	964	Hospitalized	Probably not	Not related

Dose Group	Subject No.	Serious Adverse Event COSTART term(s)	Day of Onset	Serious Category[a]	Relationship to ABT-378/ritonavir	
					Investigator	Investigator
400 mg/ 200 mg	304	Abdomen enlarged Abdominal pain Vomiting	994	Hospitalized	Probably not	Not related
		Depression	1136	Hospitalized	Not related	Not related
	308	Pancreatitis	592	Hospitalized	Not related	Probably not
		Cardiomyopathy	1155	MSI	Not related	Probably not
	309	Suicide attempt*	1093	Hospitalized	Not related	Not related
	310	Cerebral infarct	1081	Hospitalized, LT, MSI	Possible	Probably not
	326	Sinusitis	912	Hospitalized	Not related	Not related
		Accidental injury[c]	1111	Hospitalized	Not related	Not related
	363	Neuralgia[b]	-62	Hospitalized	Not related	Not related
	412	Accidental injury[c]	212	Hospitalized	Not related	Not related
	417	Encephalopathy[c]	61	Hospitalized	Probably not	Probably not
		Pneumonia	205	Hospitalized, PD	Probably not	Probably not
		Rhabdomyolysis	208	Prolonged Hosp, PD, Death	Probably not	Possibly
	420	Fever Rash	26 27	Hospitalized	Not related	Not related
	424	Anemia	1	MSI	Not related	Not related
		Anemia	8	Hospitalized, MSI	Not related	Probably not
	429	Pneumonia	1	Hospitalized	Not related	Not related
	471	Pathological fracture	99	Hospitalized	Not related	Not related
		Carcinoma of lung	126	Death	Not related	Not related

[a] MSI = Required medical or surgical intervention to prevent serious outcome; LT = Life threatening; PD = Persistent or significant disability/incapacity; Prolonged Hosp = Prolonged hospitalization.

[b] Symptoms (abdominal pain/discomfort) began prestudy.

[c] Subject No. 326: Leg injuries due to boating accident; Subject No. 401: Appendicitis; Subject No. 412: Right arm fracture; Subject No. 417: Progressive multifocal leukoencephalopathy (PML)

* Subject was prematurely discontinued for the serious adverse event.

Cross Reference: Section 14.3.3 (narratives) and Appendices 16.2__7.1 and 16.2__7.2.

List of Subjects Experiencing Serious Adverse Events – Study 720

Dose group	Subject No	Day of Onset	SAE Term	Serious Category	Relationship to LPV/RTV per investigator
200/100	104	476	Heart beat irregular, SOB, syncope	Hosp	Not related
	107	264	Drug dependence	Hosp	Not related
	111	465	Abdominal distention, pain, fever, nausea, vomiting	Hosp	Probably not
		1182	Nausea, vomiting, fever, dehydration, hypotension, tachycardia	Hosp	Not related
	121	139	Chest pain, syncope	Hosp	Not related
		805	Pneumothorax due to gun shot wound	Hosp	Not related
		1304	Chest pain, SOB	Hosp	Probably not
	131	410	Nephrolithiasis, flank pain	Hosp	Not related
		1147	Flank pain	Hosp	Probably not
	133	1092	Increasing discomfort in left hip	Hosp	Not related
400/100	101	93	Lower respiratory tract infection/fever	Hosp	Not related
	109	506	Accident, fractured clavicle and ribs	Hosp	Not related
	113	101	Rectal ulcer	Hosp	Not related
		990	Hoarseness	Hosp	Probably not
		1275	Left hemiparesis	Hosp	Probably not
		1397	Sudden onset of profound hearing loss	Hosp	Probably not
	123	364	Productive cough, pneuomia	Hosp	Not related
	128	118	Abortion	Elective abortion	Not related
		363	Abortion	Elective abortion	Not related
	130	78	Enterocolitis, fever	Hosp	Possibly
		89	Abscess	Prolonged hosp	Probably not
	207	1028	Spinal mass	Hosp	Not related
		1034	Cardiac arrest	LT	Possibly
		1044	Death of unknown cause	Death	possibly
	209	64	Appendicitis	Hosp	Probably not
	211*	15	Lymphoma	Hosp	Not related
		26	DVT	LT	Not related
	238	58	Exertional dyspnea, fatigue	Hosp, PD	Probably not
		180	Constipation	Prolonged hosp	Probably not
		881	Exertional dyspnea, productive cough	hosp	Not related
	260	242	UTI	Hosp	Not related
		1056	Hypoxemia	Hosp	Not related
	269	249	Jaundice, hepatitis	PD	Not related
	273	404	Fever of unknown origin	Hosp	Not related
		409	Lower extremity and back pain	MSI	Not related
400/200	210*	364	Alcohol detoxification	Hosp	Not related
	220	147	Pneumothorax due to gun shot wound	Hosp/LT/MI	Not related
	239	151	GI disorder	Hosp	Probably not

	245	14	Sinusitis	MSI	Not related
	256	1148	Insect bite resulting in ulcer	Hosp	Not related
	262	415	Depression	Hosp	Not related
	264	10	Dehydration, diarrhea, fever, sweats, fatigue	Hosp/ Prolonged Hosp	Probably
		169	Anemia	Hosp	Not related
		198	Abdominal pain, anemia	Hosp	Probably not
		340	Abdominal pain	Hosp	Not related
		358	Bloating, constipation, flatus, dehydration, nausea, urinary retention, vomiting, abdominal pain	Hosp	Probably not

***subject discontinued due to event**

Appendix B

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	***ODS POSTMARKETING SAFETY REVIEW***	
TO: Debra Birnkrant, MD, Division Director, Division of Antiviral Drug Products HFD-530	**FROM: Melissa M. Truffa, R.Ph. Safety Evaluator Team Leader DDRE (HFD-430)**	**ODS PID #: D040463** **DATE Completed: August 2, 2004**

DATE REQUESTED: April 19, 2004	**REQUESTOR/Phone #: Kimberly Struble, Pharm.D., Medical Officer 301-827-2367**	
DRUG (Generic): lopinavir/ritonavir	***NDA # 21-226 and 21-251***	**SPONSOR: Abbott**
DRUG NAME (Trade): Kaletra®	**THERAPEUTIC CLASSIFICATION: antiretroviral/protease inhibitor**	

EVENT: Serious Skin reactions [Stevens Johnson syndrome (SJS), erythema multiforme (EM), and toxic epidermal necrolysis (TEN)]

Executive Summary

Fourteen unduplicated cases of a serious skin reaction were retrieved from AERS postmarketing database. These include cases of Stevens Johnson syndrome; 4 cases of erythema multiforme; 2 cases of porphyria cutanea tarda; and 1 case eac of TEN, vesiculobullous rash, and severe blister. The majority (8/14, 57%) of the cases are confounded by concomitant medications such as fluoroquinolones, nevirapine, abacavir, voriconazole, and phenytoin that have been associated with serious skin reactions and were temporally related to the occurrence of the adverse reaction. Specifically, four of the five SJS cases, two of the four EM cases and the case of TEN were confounded by concomitant medications.

However, there are two foreign cases of erythema multiforme that appear to be relatively unconfounded and one case of SJS from a Kaletra early access program in Taiwan. One of the EM cases includes a rechallenge with Kaletra and tenofovir with a "prompt" reoccurrence of rash, although the details of the temporal relationship of the rechallenge are vague.

There is limited evidence in the postmarketing safety database and no reports in the literature regarding serious skin reactions with the use of lopinavir/ritonavir. The two cases of erythema multiforme, especially the rechallenge case, if supported by additional cases in the medical officer's review of the Kaletra early access program could be adequate evidence to consider adding EM to the Postmarketing Experience section of the Kaletra label.

Reason for Request/Review

After identifying reports of serious skin reactions in Kaletra's Early Access Program (EAP) and the QD vs. BID Kaletra clinical trial, Dr. Struble was interested in postmarketing reports of serious skin reactions with the use of Kaletra, specifically, Stevens Johnson syndrome and erythema multiforme.

Relevant Product Labeling

With the exception of exfoliative dermatitis, there is no mention of more severe rashes in the current Kaletra product labeling.

Adverse Reactions

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.

- *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.

Search Dates: April 19, 2004	**Search Type(s): [X] AERS [X] Literature ☐ Other**

Search Criteria
Drug Name: Kaletra® (lopinavir/ritonavir)
Generic: lopinavir
MedDRA Terms: ODS Reaction List for Serious Skin (29 PTs) including Stevens Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis.

Search Results
As of April 19, 2004, a total 22 reports of serious skin reactions with the use of lopinavir/ritonavir were retrieved form the Adverse Event Reporting System (AERS). After merging duplicates and excluding 2 reports because the patients were not taking Kaletra at the time of the event, 14 unduplicated cases were identified. Two of the14 cases are from Early Access programs (SJS-1 and PCT-1).
There are a total of 1841 safety reports in AERS for lopinavir/ritonavir.

Summary of Data: (n=14)

Gender:	Males = 10, Females = 3, Unknown=1
Mean Age (n=13):	45.7 years (range 35-62)
Location:	5-US and 9-Foreign (4-France, 1- Canada, Portugal, Sweden, Taiwan, and UK)
Year of Event:	2000-2; 2001-4; 2002-4; 2003-3; 2004-1
Outcome:	Death-2, Hospitalization-7, Required intervention-4, Other-1

Dechallenges-8, Rechallenge-1
Mean duration of therapy: 30 days* (range 1 day to 5 month) *The outlying of 16M was not included in this calculation.
Reported event: SJS-5, erythema multiforme-4, porphyria cutanea tarda-2, TEN-1, vesiculobullous rash-1, and blister-1

Date of Approval:	September 2000
Indication:	Treatment of HIV infection

Summary of erythema multiforme and Stevens Johnson Syndrome cases

Erythema multiforme (n=4)

Four postmarketing cases of erythema multiforme were reported with the use of lopinavir/ritonavir. The following two cases are notable

AERS Case# 4049917, United Kingdom, 2003: On approximately 20 Nov 2003, the patient experienced a Bactrim rash. Although the report does not state that Bactrim was discontinued it is implied. On 21 Nov 2003, the patient began lopinavir/ritonavir, tenofovir and lamivudine. On 29 Nov 2003, the patient experienced erythema multiforme and was treated with an antihistamine and topical steroids. The patient was not hospitalized. The dermatologist suspected the erythema multiforme was drug related. However, the reporter stated that the erythema multiforme may have been due to an infection. So on 08 Dec 2003, the patient was rechallenged with Kaletra, tenofovir, and lamivudine. On an unknown date, the patient experienced a prompt recurrence of rash and Kaletra and tenofovir were discontinued. The patient was switched to stavudine, ritonavir, saquinavir, and continued lamivudine. There has been no recurrenc of the rash.

AERS Case#4121258, Canada, 2004: On 26 Feb 2004, a 45-year old male started Kaletra for HIV infection. Concomitant medications include lamivudine, Oxycocet, oxycodone HCl, Bactrim, valproate, lorazepam, and amitriptyline. The patient was previously exposed to ritonavir in 1999 and developed a generalized rash. On 07 Mar 2004, the eleventh day after beginning Kaletra, th patient experienced erythema multiforme, pain, pruritus, headache, and generalized malaise. Four days later on 11 Mar 2004, the patient's symptoms worsened and he experienced erythematous maculopapules; vesicles with bubbles; desquamation; and hemorrhagic lesions to the neck, scalp, abdomen, legs, arms, palms, and armpits. There were no lesions inside the mouth or eyelids. On 11 Mar 2004, the patient visited the doctor and Kaletra was discontinued. The patient was treated with Prevex, Aveeno powder, prednisone 50 mg daily for 5 days, and the dosages of oxycodone were increased. On an unknown date, the patient recovered from erythema multiforme, pain, and pruritus.

Both patients recovered after Kaletra was discontinued (a positive dechallenge). One patient had a "prompt" reoccurrence of his rash when rechallenged with Kaletra, lamivudine, and tenofovir. The rash resolved after Kaletra and tenofovir were discontinued, although th details of the temporal relationship of the rechallenge are vague. This patient also had a rash to Bactrim one day prior to starting antiretroviral therapy. The second patient had a history of rash with a previous exposure to ritonavir that could have sensitized him to Kaletra.

The third and fourth cases of EM are confounded by concomitant medications. Both patients were receiving abacavir and one was diagnosed with a suspected abacavir hypersensitivity reaction; the other case of EM was suspected as due to phenytoin. However, the reporter speculated that this AE may have been triggered by a drug interaction between Kaletra and phenytoin that resulted in elevated phenytoin drug levels.

Stevens Johnson Syndrome (n=5)

Five postmarketing cases of SJS were reported with the use of lopinavir/ritonavir. One is from the US and 4 are non-US cases. Of thes five cases of SJS, four are confounded by concomitant medications (fluoroquinolones-2, voriconazole-1, and nevirapine) that have been associated with Stevens Johnson syndrome.

In the first case, voriconazole was started 4 days before Kaletra and saquinavir were added to the patient's antiretroviral therapy. Two weeks into the voriconazole therapy and 1 week into therapy with Kaletra, the patient developed a fever and a total body rash. Kaletra and saquinavir were discontinued as a possible cause; however, 4 days later the symptoms worsened with rash, fever, myalgia and conjunctivitis. Voriconazole was discontinued; the patient was treated with diphenhydramine and steroids. The patient recovered and was diagnosed with SJS secondary to voriconazole. Serious cutaneous reactions, including Stevens Johnson Syndrome, erythema multiforme, and toxic epidermal necrolysis have been reported with voriconazole therapy. A second patient was diagnosed with SJS, one month and three weeks after starting Kaletra and moxifloxacin, respectively. Moxifloxacin, Kaletra, and the patient's concomitant TE medications were discontinued. SJS was suspected as due to the fluoroquinolone which is labeled for SJS; however, Kaletra cannot be ruled out because of the temporal relationship and the positive dechallenge when Kaletra was discontinued. A third patient treated with Kaletra and tenofovir for about a month and abacavir for five months was diagnosed with a Shigella infection and treated with ciprofloxacin for 7 days. The day after finishing the course of Cipro, he experienced the beginnings of a cutaneous eruption on the inner thigh and abdomen with associated pruritus, gingivostomatitis and fever. He experienced 15% detachment of the corporeal area of the hands, feet, and anterior face of the thigh with acute pain. His thigh, hands, and feet lesions were "confluence", and he was diagnosed with Stevens-Johnson syndrome by biopsy. A fourth patient developed SJS two weeks after Kaletra, nevirapine, and lamivudine were started. Antiretrovirals were discontinued and the patient improved after a two week hospitalization. Stevens Johnson Syndrome has been associated with the use of nevirapine and is a labeled event.

There is one relatively unconfounded case of SJS from 2001. This patient was enrolled in Kaletra expanded access study in Taiwan. Kaletra, didanosine, stavudine, and indinavir replaced stavudine, lamivudine and nevirapine. Two weeks later the patient experienced fevers, dyspnea, and desquamated skin at multiple foci of the ear lobes, trunk and face with ulcers of the oral mucosa, anal region, and urethra. Blood cultures were positive for klebsiella pneumonia and E. coli. The patient condition deteriorated and he died of suspected agranulocytosis, septic shock, SJS, and acute pancreatitis. No autopsy was performed.

Literature Review:
A broad PubMed search of all skin diseases in association with Kaletra or the combination of lopinavir and ritonavir retrieved one article that was not relevant because it described a case of alopecia.

Irrespective of Kaletra, PubMed was searched for articles discussing porphyria cutanea tarda. The following three articles refer to risk factors associated with porphyria cutanea tarda.

1. Sams H, Kiripolsky MG, et al. Porphyria cutanea tarda, Hepatitis C, alcoholism, and hemochromatosis: a case report and review of the literature. Cutis. 2004 Mar;73(3):188-90.
2. Drobacheff C, Derancourt C, et al. Porphyria cutanea tarda associated with human immunodeficiency virus infection. Eur J Dermatol. 1998 Oct-Nov;8(7):492-6.
3. O'Connor WJ. Porphyria cutanea tarda and HIV: two cases associated with hepatitis C. AIDS Patient Care STDS. 1998 May;12(5):341-6.

Discussion
A total of fourteen unduplicated postmarketing cases of a serious skin reaction were retrieved from AERS that include Stevens Johnson Syndrome (5), erythema multiforme (4), TEN (1), porphyria cutanea tarda (2), vesiculobullous rash (1), and severe blister (1). The majority of these cases are confounded by concomitant medications whose initiation and discontinuation had a temporal relationship to the occurrence of the serious skin adverse reaction. In many of the confounded cases, initiation of antiretroviral therapy that included Kaletra and resolution of the adverse event after discontinuation of Kaletra and other suspect medications were temporally related, making it difficult to completely rule out Kaletra. Five of the 14 cases were from the US; however, it should be noted that the two relativel unconfounded cases of EM and the case of SJS were all foreign reports.

In addition to the EM and SJS cases there were also two notable cases of porphyria cutanea tarda (PCT) or non-acute porphyria. The first patient started Kaletra and Combivir and one month later was hospitalized with porphyria cutanea tarda with lesions mostly on the upper extremities. Kaletra was discontinued and the event resolved with treatment. Combivir continued. The patient was HCV negative and did not have any risk factors such as estrogen use. She did have a history of HIV hepatitis. The second case of PCT involved a patient enrolled in an EAP who was taking Kaletra, efavirenz, abacavir and indinavir. About 6 weeks after starting antiretrovirals the patient developed multiple blisters on his hands. He had experienced blisters "occasionally" on his hands in the past but never to this extent. PCT was diagnosed based on a skin biopsy and the antiretrovirals including Kaletra were discontinued and the blister showed "immediate improvement". In the study investigator's opinion the patient may have had some underlying etiology that was exacerbated b Kaletra. The patient was HCV negative, was not exposed to any occupational or social agents, nor were there any hereditary disorders or allergic reactions that could be considered as alternative etiologies. Both patients improved when lopinavir/ritonavir was discontinued and neither patient had any documented risk factors.

Porphyria cutanea tarda has been associated with alcohol use, HCV, estrogens, occasionally chlorinated hydrocarbon, and less commonly with HIV.[1,2,3] AERS was also searched for cases of PCT with the other antiretrovirals. Eight unduplicated cases were retrieved. Three with zidovudine, 2 with nevirapine, 1 each with indinavir, amprenavir, and nevirapine/tenofovir. None of these cases wei notable.

Conclusion
The majority (8/14, 57%) of the cases were confounded by concomitant medications (fluoroquinolones-2, nevirapine-2, abacavir-4, voriconazole-1, and phenytoin-1), all of which have been associated with serious skin reactions. However, there are two foreign cases o erythema multiforme that appear to be relatively unconfounded and one case of SJS from an EAP in Taiwan. One of the EM cases includes a rechallenge with Kaletra and tenofovir with a "prompt" reoccurrence of rash, although the details of the temporal relationship c the rechallenge are vague.

There is limited evidence in the postmarketing safety database and no reports in the literature regarding serious skin reactions with the use of lopinavir/ritonavir. The two cases of erythema multiforme, especially the rechallenge case, if supported by additional cases in the medical officer's review of the Kaletra early access program could be adequate evidence to consider adding EM to the Postmarketing Experience section of the Kaletra label.

Although the two cases of porphyria cutanea tarda are intriguing, DDRE would not recommend adding PTC to the label at this time. We will also continue to monitor the AERS database for new cases of PCT with Kaletra and other antiretrovirals.

Reviewer's Signature / Date: /s/ Melissa M. Truffa, R.Ph. July 30, 2004	
Division Director Signature / Date: /s/ Min Chen, R.Ph., M.S. for Mark Avigan, M.D., August 2, 2004	

The table below summarizes the serious skin reactions reported to AERS.

Table 1: Kaletra and Serious Skin reactions (n=14)
April 2004

	MFR #	AERS Case #	Age/ Sex	Out-come	Event Year/ Loc	Event	Drug/ Duration	Concomitant Meds	Comments/ Other events
1.	2003002270	3931910	48M	HO	2002 WI	SJS	Kaletra/SQV x 1 week TDF/ZDV/3TC/ EFV x 2M	voriconazole griseofulvin prednisone nicotinic acid ASA Tramadol Gabapentin amitriptyline topiramate atenolol Bactrim bupropion oxycodone	HX of biopsy proven vasculitis with painful peripheral neuropathy. 20Nov02: voriconazole started, pt on high-dose steroids. 25Nov02: Kaletra and SQV added 05Dec: 2 wks into voriconazole therapy and 1 wk into Kaletra therapy, fever, total body rash. Kaletra/SQV dc'd as possible cause. 09Dec02: Symptoms worsened with ulcer, rash, fever myalgia, conjunctivitis voriconazole dc'd. Started diphenhydramine and steroid dose increased. Symptoms resolved and the patient was DX'd with SJS secondary to voriconazole.
2.	200310104BFR	3992056	49M	HO DS	2002 France	SJS hepatitis	Kaletra/ddI/d4T x 1M	moxifloxacin ciprofloxacin ethambutol Rifabutin INH omeprazole bromazepam zopiclone AmphoB pentamidine	Pt treated with moxifloxacin for 2 weeks then Cipro x 4 days (stock shortage) then moxifloxacin was reintroduced. 23Dec02: 3 weeks after starting therapy with a fluoroquinolone and approximately 1 month after starting Kaletra, pt Dx'd with SJS. FQ, ARVs and TB medications were stopped. The patient recovered from the SJS. First two weeks of Jan 03, patient with fever, pancytopenia and increased LFTs. EFV/TDF/d4T/ddI restarted. SJS suspected due to fluoroquinolone, however, Kaletra cannot be ruled out because of the positive dechallenge when discontinued.
3.	01P-056-0108507-00, 200114314FR, B0114287A	3679326 3679761 3682801	37M	HO	2001 France	SJS	Kaletra/TDF x 1 month ABC x 5 M	metronidazole amoxicillin ciprofloxacin cefuroxime	One month after starting Kaletra/TDF, severe pyretic diarrhea with colic and vomiting. ARVs interrupted and treated with cefuroxime and silicates. After 1 dose, immediate vomiting. 2 days later the patient experienced bloody, glairy mucus in feces was hospitalized and treated with amoxicillin and metronidazole for suspected infection. Restarted ARVs and a few days later DX'd with Shigella infection and treated with Cipro for 7 day. The day after finishing the course of Cipro, experienced the beginning of cutaneous eruption of the internal face of the thigh, of the abdomen, associated with pruritus,

									gingivostomatitis and fever. 3 days la with maculo-papulosis erythematous lesions in rosette, with fingers vesicular lesions, and scrotal erosion were present. The patient had no occular lesions. ARVs were again stopped. The patient experienced 15% detachment of corporeal area of the anterior face of the thigh, hands, and feet, and acute pain and his thigh, hands, feet lesions were "confluence". There were no new lesions. The patient was diagnosed with Stevens-Johnson syndrome by biopsy. Event resolved about 10 days later.
4.	01P-150-0108551-00	3681068	37F	HO	2001 Sweden	SJS	Kaletra/NVP 3TC x 2 weeks d4T x years	Bactrim	2 weeks after starting Kaletra/NVP/3TC, Pt experienced vesicles and pruritus on her lips was hospitalized and diagnosed with SJS described as vesicles and rash on her lips, urethral and vaginal mucosa. Conjunctivitis and big vesicles on the feet were also noted. ARVs dc'd and she was treated with parenteral nutrition, topical peanut oil and prednisolone eye drops. The patient's skin and general condition improved, and she was discharged with scaly hands and crusts on her lips, after two weeks of hospitalization.

5.	01P-153-0105905-00	3648305	53M	DE	2001 Taiwan	agranulocytosis sepsis SJS pancreatitis	Kal[illegible]ddI/d4T/ IDV x 2 weeks	Megace Bactrim fluconazole	**Kaletra EAP Study** HX of MAC and episode of disseminated MAC (Feb 2001) 29Mar01: Kaletra/ddI/d4T/IDV replaced d4T/3TC/NVP 03 Apr 01: with symptoms of diarrhea, chest tightness and decreased appetite. Megestrol acetate was added. 13Apr01: fevers, dyspnea, and altered consciousness. The patient appeared to have diffuse abdominal tenderness. The skin desquamated at multiple foci of the ear lobes, trunk and face, with an approximate size of 2-3 on in diameter. There were ulcers of the oral mucosa, anal region, and urethral orifice. Skin biopsy or bone marrow studies were not performed because of his critical condition. No report was available from his family members as to when the skin or mucosa lesions start to develop, recent use of any other herbal remedies or NSAIDS or recent flu-like symptoms. Leukocyte count was 400/mm3, hematocrit 28.7, and platelet 13,000/mm3 on entry, and was 40/mm3, 20.3% and 14,000/mm3. Chest radiography revealed consolidation at the both upper lobes. Blood cultures =K. pneumonia and E coli with an identical, antibiogram with the respective sputum isolates in Mar 2001. lactic acid level was 9.06 mmole/L and amylase level, 669 IU/L and lipase was 330 IU/L His condition deteriorated with hypotension, coagulopathy and metabolic acidosis, despite use of blood transfusion, ceftazidime, and fluconazole 14 Apr 2001. PT expired Autopsy was not performed. The clinical presentations were consistent with agranulocytosis with septic shock due to E coli and K pneumonia, Stevens Johnson syndrome, and acute pancreatitis.
6.	03P-167-0244108-00 B0318313A	4049917 4053582	UNK	RI	2003 UK	erythema multiforme	Kaletra/TDF/3TC x 8 days	Bactrim	20Nov03: Bactrim rash 21Nov03: Kaletra/3TC/TDF started 23Nov03: Recovered from Bactrim Rash 29Nov03: Developed EM that was suspected as drug-related by dermatologist. Treated with antihistamine and topical steroids. 08Dec03: rechallenged with Kaletra/TDF/3TC and on an unknown

									date experienced a prompt recurrence rash. On an unknown date, Kaletra and TDF dc'd. Switched to d4T/3TC/SQV/RTV with no recurrence of the rash.
7.	04P-028-0254034-00	4121258	45M	RI	2004 Canada	erythema multiforme	Kaletra x 12 days 3TC	oxycodone Bactrim valproate lorazepam amitriptyline	11 days after starting Kaletra, pt experienced erythema multiform, pain, pruritus, headache, and generalized malaise. Four days later the symptoms worsened with erythematous macules, papules, vesicles with bubbles, desquamation, and hemorrhagic lesions to the neck, scalp, abdomen, legs, arms, palms, and armpits. There were no lesions inside of the mouth or eyelids. The patient visited the doctor and Kaletra was discontinued. The patient was treated with Prevex, Aveeno powder, steroids and increased doses of his narcotics.
8.	02P-130-0193922-00	3801895	45M	RI	2002 Portugal	erythema multiforme drug hypersensitivity	Kaletra/ABC x 12 weeks d4T x unknown duration	none reported	12 weeks after starting Kaletra and ABC, the patient developed generalized pruritic erythema multiforme (grade II toxicity). Discontinued abacavir and stavudine at his own accord and 2 days later the patient was seen at the clinic and the rash was ongoing. A skin biopsy was not performed. No further symptoms were apparent and a diagnosis of moderate hypersensitivity to abacavir was made. Kaletra was also dc'd. Mild improvement of the rash followed.
9.	A0157123A	369692	58F	HO	2001 TX	erythema multiforme	Kaletra/ABC/ APV x 2 doses	phenytoin x 1M Atovaquone gatifloxacin	HX of rash of unknown etiology (NVP, Bactrim and Dapsone were suspected) Pt switched from NFV/Combivir to Kaletra/ABC/APV. After 2 dose of abacavir and Kaletra and 1 month of phenytoin, Pt with itchy skin. ARVs dc'd but phenytoin continued for approximately 3 weeks, when she was later seen with a high fever and bad rash. Suspected pneumonia and initiated gatifloxacin and Eucerin cream. Patient had a total body rash which was suspected to be erythema multiforme with fever (up to 104 degrees Fahrenheit) and chest X-ray changes consistent with PCP. Subsequently, her regular physician reported that she was not hypoxic and had no evidence of pneumonia on her chest X-rays. She did have elevated liver function tests. The patient did not have mucosal

									involvement, respiratory difficulty, diarrhea, nausea, vomiting or hypotension. Transferred to Derm unit worsening rash and dehydration. Where a dermatologist believed the rash due to phenytoin which may have been triggered by an elevation in concentration due to Kaletra. The patient had no mucosal involvement (vaginal, nasal and oral mucosa were examined). At the time of reporting, the patient had no fever, her liver function tests were improved and her rash was at the peeling stage. Abacavir will not be restarted.
10.	04P-056-0248945-00	4091257	38 M African	DE	2003 France	TEN	Kaletra/NVP x 10 days	UNK	Recently diagnosed with HIV 10Dec03: Started Kaletra and NVP 20Dec03: Buccal aphthosis treated with fluconazole and ketoprofen 21Dec03: fever, urticaria, facial edema, and conjunctivitis and suspected SJS. 26Dec03: Experienced skin detachment involving ears, face, upper limbs, thorax, and axilla and was diagnosed with TEN Also experienced 100% epidermal detachment, lesions of the upper GI tract, and ocular lesions. Kaletra dc'd on an unknown date. 07Jan04: PT died due to sepsis to pyocyaneous bacillus with multi-organ failure.
11.	04P-163-0248449	4090248	38F	HO	2003 FL	Porphyria cutanea tarda	Kaletra/3TC/ZDV x 2M	nefazodone levothyroxine fluconazole dronabinal	Jul 03: started Kaletra 1 month later in Aug2003, patient hospitalized with Porphyria cutanea tarda (lesions mostly on upper extremities. Treated with sulfadiazine and unspecified lotion. Sept03: Kaletra dc'd Combivir continued. Oct 03: Event resolved. The patient does not have any risk factor such as estrogen use.
12.	00P-163-0096040-00	3670674	35M	RI	2000 US	Porphyria cutanea tarda	Kaletra/EFV/ABC/IDV x 1.5 M	pentamidine loratadine clarithromycin acyclovir	EAP Study Mar00: started Kaletra/EFV/ABC/IDV On 08 May 2000, developed multiple blisters on the dorsum of his hands. The patient had experienced blisters "occasionally" in the past on his hands, but not to this extent. Blisters developed any place the patient had contact, similar to a dermatitis reaction. The blisters were 1 cm in diameter that became increasingly painful, and the patient could not wear gloves to protect his

									hands. DX of Porphyria Cutanea Tar (PCT) made on the basis of skin lesion biopsies. The patient was advised to stay out of the sun because his skin became hypersensitive. On 24 Jul 2000, the patient was advised to stop ARVs including Kaletra. The blisters showed "immediate improvement." There were no plans to reintroduce Kaletra. In the sub investigator's opinion, the patient may have had some underlying etiology that was exacerbated by Kaletra. According to the site, this event was not caused by other medications, and the patient was not exposed to any social or occupational agents. In addition, hepatitis C, hereditary disorders, or allergic reaction are not alternative etiologies. No seasonal allergies or family history relevant to this event. It was noted that "April 2000 was the patient's first complaint of this event." He had not started on any other medications at the time of this event. The patient was treated with Chloroquine and was considered to be improved on 30 Oct 2000.
13.	11959848	3822156	49M	OT	2002 US	blister pruritus	Kaletra/d4T/FTC x 16 M	Celebrex x 15 months	Developed medically serious (grade 3) blisters on 21 Jun 02, 16 months after starting ARVs. Pt with "blisters" described as "itching, fluid filled, blisters, the size of a cigarette butt". He had a total of 5-6 located on his abdomen and dorsal foot, toe, back, and thigh. He denied involvement of his mucus membranes and stated that he did have some peeling of the hand and feet that was about a year old. He was recently treated for "bronchitis" about one month prior to this event with what sounded like a Z-pack. He continued to have a cough and nightsweats. He reported his last PPD test was 3 months earlier and was negative. Study therapy was interrupted on 21 Jun 02 due to the event. The event was ongoing at the time of the report. A dermatology appointment was scheduled for 02 Jul 02.
14.	01P-056-0103677-00	3614429	62M	HO	2000 France	vesiculobullous rash	Kaletra/ABC/3TC x 2.5 M	Bactrim fluconazole	2.5 months after starting ARVs including Kaletra, cutaneous eruption and fever. 2 weeks later hospitalized with CMV antigenemia, cutaneous eruption and fever. A 2 week course of ganciclovir

									was started. The day after ganciclovi course completed, reappearance of eruption on inferior limbs and aggravation of bulla. One week later abacavir stopped and eruption regressed. Kaletra continues.

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Team Leader's Memorandum

NDAs:	21226, 21251
Drug and Indication:	Kaletra® (lopinavir/ritonavir) in combination with other antiretroviral medications for the treatment of HIV-1 infection
Dose:	lopinavir/ritonavir 400/100 mg twice daily
Date submitted:	December 19, 2003
Date of MO review:	September 13, 2004
Date of Memorandum:	October 19, 2004

Background

Kaletra® is a co-formulation of two protease inhibitors, lopinavir (LPV) and ritonavir (RTV). In this drug combination, LPV is the active antiretroviral agent and RTV serves as a pharmacologic enhancer for LPV. RTV inhibits the metabolism of LPV via the CYP3A metabolic pathway, thereby increasing LPV exposure. Soft gel capsule and oral solution formulations of Kaletra received accelerated approval on September 15, 2000. Accelerated approval was based on results from one phase 3 trial in antiretroviral-naïve patients and an interim phase 3 report of a study of protease inhibitor (PI) experienced subjects. These studies showed significant declines in HIV-1 RNA levels and increases in CD4 cell counts over 24 weeks. Results from three phase 1/2 trials, including studies M97-720 and M97-765, were also provided. Reviews of efficacy supplements containing 48-week data from an adult phase 3 clinical trial and interim data from an ongoing pediatric study were completed in January, 2002. Traditional approval was granted in November 2002.

This supplemental application contains long-term efficacy and safety data from two of the three previously submitted phase 1/2 trials. Study M97-720 is updated to include 204-week efficacy and safety results in antiretroviral-naïve subjects. Study M97-765 is updated to include 144-week efficacy and safety results in antiretroviral-experienced subjects. In addition, results of a multiple dose study in HIV and HCV co-infected subjects with mild to moderate hepatic impairment and Week 104 mice and rat data were submitted.

No new dosing recommendations or indications are sought with this supplemental application.

Efficacy

Study M97-720
This was a randomized, multi-center study of LPV/RTV in combination with stavudine (d4T) and lamivudine (3TC) in HIV-infected subjects. Thirty-two antiretroviral-naïve subjects with HIV RNA ≥ 5,000 copies/mL were randomized in group I to receive one of the following blinded treatment regimens:

Group I:

LPV/RTV 200/100 mg BID + d4T + 3TC
LPV/RTV 400/100 mg BID + d4T + 3TC

Following a safety review after four weeks of dosing by the first 16 subjects in group II, 68 subjects were randomized to one of the following blinded treatment arms.

Group II:

LPV/RTV 400/100 mg BID + d4T + 3TC
LPV/RTV 400/200 mg BID + d4T + 3TC

All subjects continuing on treatment at Week 48 were converted to open-label LPV/RTV 400/100 mg BID between Weeks 48 and 72.

The study population was predominately male (96%) and had a mean age of approximately 35 years. Non-white racial groups comprised 30% of the population. The median baseline HIV RNA level for all randomized subjects was 4.92 $\log_{10}$ copies/mL and was comparable between treatment regimens. Forty-five percent of subjects had baseline HIV RNA levels ≥ 100,000 copies/mL. The median baseline CD4 cell count was 326 cells/mm^3.

The primary efficacy outcome measure was proportion of subjects with HIV RNA < 400 copies/mL at Week 24 and the duration of response through Week 48. For the long-term follow-up analyses, the primary endpoint was extended to Week 204. FDA review of this data focused on "Time to Loss of Virologic Response (TLOVR)" analyses and proportion undetectable analyses.

Through four years of follow-up, antiretroviral-naïve subjects receiving LPV/RTV achieved and maintained durable HIV RNA suppression and significant increases in CD4 cell counts. At Week 204, 71% and 70% of subjects achieved HIV RNA < 400 copies/mL and < 50 copies/mL, respectively. In a subgroup analysis, the proportion of patients with HIV RNA < 400 copies/mL through 204 weeks was about 80% among patients first assigned to receive LPV/RTV 400/100 mg bid and was numerically higher than those patients first assigned to receive LPV/RTV 400/200 mg bid (61%). The difference is primarily due to more subjects first assigned to LPV/RTV 400/200

discontinuing for virologic failure (4 versus 1 subjects) and for "other" reasons (6 versus 3 subjects).

In addition, statistically significant increases in CD4 cell counts were observed for all subjects at each study visit. The mean change from baseline at Week 204 was 440 cell/mm^3.

Study M97-765
This was a blinded, randomized, multi-center trial in seventy antiretroviral-experienced subjects with HIV RNA levels between 1,000 and 100,000 copies/mL. Subjects were:

- NNRTI naïve
- naïve to at least one NRTI
- currently receiving a PI and one or two NRTIs that had not changed in the last 12 weeks prior to enrollment

Subjects were randomized to one of the following dose groups:

Group 1: LPV/RTV 400/100 mg BID
Group 2: LPV/RTV 400/200 mg BID

The PI in each subject's existing regimen was discontinued on day –1. For days 1-14, subjects received their assigned LPV/RTV regimen in combination with the NRTIs received in their existing regimen. The study was designed in this manner to isolate the effect of LPV/RTV on HIV RNA reduction over two weeks. On Day 15, each subject received a new NRTI regimen that included at least one new NRTI not previously received. Nevirapine was also added to each subject's regimen on Day 15.

In general, baseline characteristics for all randomized subjects were comparable between treatment regimens. The study population was mostly male (90%) and had a mean age of about 40 years. Non-white racial groups comprised 27% of the population. The median baseline HIV RNA level for all randomized subjects was 4 $\log_{10}$ copies/mL and was comparable between treatment regimens. The median baseline CD4 cell count was 371 cells/mm^3.

Due to the small sample size, efficacy analyses focused on proportions of subjects who achieved HIV RNA below the limits of quantification. No statistically significant differences were observed between the dose groups for the analyses of proportion of subjects with HIV RNA < 400 copies/mL or < 50 copies/mL. The proportion of subjects with HIV RNA < 400 (< 50) copies/mL at Week 144 was 53% (47%) in subjects receiving LPV/RTV 400/100 and 56% (53%) in subjects receiving LPV/RTV 400/200.

Although the proportions of subjects with HIV RNA below the limits of detection were similar between treatment arms, significant differences in phenotypic susceptibility to LPV/RTV existed at baseline. Mean fold change in EC_{50} to LPV/RTV relative to wild type virus was 1.7-fold for the 29 viral isolates from subjects in the 400 mg/100 mg dose group and 3.9-fold for the 30 viral isolates from subjects in the 400 mg/200 mg dose

group (p=0.083). Additionally, a higher percentage of subjects in the 400 mg/200 mg dose arm demonstrated baseline viral isolates with a ≥ four-fold increase in EC_{50} to LPV/RTV relative to wild type virus compared to subjects in the 400 mg/100 mg dose arm (30% vs. 7%; p=0.04).

Statistically significant increases in CD4 cell counts were observed for both dose groups compared to baseline through Week 144. The mean increase in CD4 cell counts from baseline was 177 cells/mm^3 and 249 cells/mm^3 for the 400/100 mg and 400/200 mg dose groups, respectively.

Resistance
Results of genotypic analysis were available on 11/16 subjects who experienced virologic failure in the treatment-naïve study. Baseline mutations and phenotypic susceptibility were also available on 28 patients receiving LPV/RTV 400/100 in the treatment-experienced study. No new information was obtained from analyses of this data to further characterize the impact of genotypic mutations on virologic response to LPV/RTV 400/100.

Safety
In study M97-720, 100 subjects received any dose of LPV/RTV in combination with d4T/3TC for a median of 1472 days (range 22-1472). In study M97-765, 70 subjects received any dose of LPV/RTV in combination with nevaripine and two NRTIs for a median of 1,087 days (1-1176).

Overall, the rate and pattern of adverse events (AEs) and laboratory abnormalities were similar to those identified in the original and supplemental NDAs. In both studies, the most commonly reported AEs were related to GI disorders, including diarrhea, nausea and abnormal stools. Although not new, additional cases of serious skin reactions were reported through the Adverse Event Reaction System (AERS), leading to the addition of Stevens Johnson Syndrome and erythema multiforme events to the Adverse Reaction section of the package insert.

One death occurred in study M97-720. The subject died at Week 149, one day after discontinuing study medication. The patient experienced sudden death at home one day after hospital discharge. The patient had been hospitalized for surgical evaluation of a spinal cord mass and the surgery was complicated by a peripoperative MI. The etiology of the mass was unknown but presumed to be TB. This event was considered possibly related to study medication.

Two deaths occurred in study M97-765. One subject died of metastatic lung cancer; his death was considered not related to study medication. The second subject was hospitalized with pneumonia and rhabdomyolysis after seven months on study. The patient died eight days after hospitalization from progressive renal failure. These events were considered possibly related to study drug.

Nine subjects in each study prematurely discontinued due to an AE. In study M97-720, six subjects prematurely discontinued for events probably or possibly related to

LPV/RTV. These events were related to increases in cholesterol, ALT/AST, hepatomegaly and diarrhea. In study M97-765, five subjects prematurely discontinued for events noted to be probably or possibly related to LPV/RTV by the investigator. AEs related to GI disorders contributed to premature discontinuation for four of the five subjects. One subject prematurely discontinued due to rash. Of note, the rash occurred after 33 days of dosing with LPV/RTV and after six days of dosing with nevirapine. No new or unexpected AEs leading to premature study discontinuation were observed.

Laboratory Abnormalities

No new treatment related laboratory abnormalities were noted in this review. No new findings regarding elevations in glucose were observed. Two subjects in study M97-720 and one subject in M97-765 initiated treatment with oral hypoglycemics during the study. As expected, significant proportions of subjects in each study developed lipid abnormalities. A total of 20 subjects in study M97-720 and 18 subjects in M97-765 initiated treatment with an antihyperlipidemic agent. Overall, 11 subjects in study M97-720 and 13 subjects in study M97-765 developed grade 3/4 increases in transaminases. Two subjects in study M97-720 and one subject in study M97-765 prematurely discontinued study due to elevated transaminase values. These findings are consistent with previous studies in antiretroviral-experienced and naïve subjects.

Conclusion

Study M97-720 provides long-term efficacy and safety data through 204 weeks in HIV-infected treatment-naïve patients. M97-765 provides long-term efficacy and safety data through 144 weeks in HIV-infected treatment-experienced patients. No new safety issues were identified in this supplemental application. The package insert will be updated with the long-term safety and efficacy data from these studies.

Kendall Ann Marcus, M.D.
Medical Team Leader, DAVDP

Concurrence:
HFD-530/DivDir/Birnkrant

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-014
21-251 / S-010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-226 SE8-014
TYPE: Efficacy supplement
DRUG: Kaletra
SPONSOR: Abbott

REVIEWER: Yuanchao (Derek) Zhang
TEAM LEADER: Kellie Reynolds
SUBMISSION DATE: 12-19-2003
DRAFT REVIEW: 08-27-2004

Executive Summary

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted and has concluded that the information provided is adequate to make proposed labeling revisions, with the following suggested changes to the existing Kaletra labeling.

Recommendations

The data provided in this submission support the sponsor's labeling revisions regarding the pharmacokinetic information in patients with mild and moderate hepatic impairment.

In addition, the sponsor needs to incorporate the following changes in the labeling related to Clinical Pharmacology and Biopharmaceutics:

1. CLINICAL PHARMACOLOGY: Drug-Drug Interactions: Please refer to the tenofovir and fosamprenavir package inserts and include the results from the lopinavir/ritonavir and tenofovir and lopinavir/ritonavir and fosamprenavir/ritonavir interaction studies.
2. PRECAUTIONS: Drug Interactions: Please update Table 9 to include the following information

Concomitant Drug Class: Drug Name	Effect on concentration of lopinavir or Concomitant Drug	Clinical Comment
Nucleoside Reverse Transcriptase Inhibitors: Tenofovir	↑ tenofovir	KALETRA increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving KALETRA and tenofovir should be monitored for tenofovir-associated adverse events.
HIV-Protease Inhibitors: Fosamprenavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse events has been observed with coadministration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.

		[redacted]
PDE5 inhibitors: Sildenafil Tadalafil Vardenafil	↑ Sildenafil ↑ tadalafil ↑ vardenafil	Use [redacted] sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use tadalafil with caution at reduced doses of 10 mg every 72 hours with increased monitoring for adverse events Use vardenafil with caution at reduced doses of no more than 2.5 mg every 72 hours with increased monitoring for adverse events.
Oral Contraceptive: ethinyl estradiol	↓ Ethinyl estradiol	Because contraceptive steroid concentrations may be altered when KALETRA is coadministered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended

Summary of Clinical Pharmacology Findings

The purpose of this supplement is to modify the Kaletra labeling to incorporate 204-week information from clinical study M97-720, entitled "Phase I/II Study of ABT-378/Ritonavir in Combination with Reverse Transcriptase Inhibitors in Antiretroviral Naïve HIV-Infected Subjects" and the hepatic impairment study M01-347, entitled "Evaluation of the multiple dose pharmacokinetics of lopinavir/ritonavir in HIV infected subjects with mild and moderate hepatic insufficiency".

Changes related to Clinical Pharmacology and Biopharmaceutics are being proposed to incorporate pharmacokinetic information on patients with mild and moderate hepatic impairment.

The sponsor proposed the following labeling changes related to Clinical Pharmacology and Biopharmaceutics:

1. CLINICAL PHARMACOLOGY: Special Populations: Hepatic Impairment: Add "Multiple dosing of KALETRA 400/100 mg twice daily to HIV and HCV co-infected patients with mild to moderate hepatic impairment (n=12) resulted in a 30% increase

in lopinavir AUC and 20% increase in C_{max} compared to HIV-infected subjects with normal hepatic function (n=12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31%, respectively). Caution should be exercised when administering KALETRA to subjects with hepatic impairment. KALETRA has not been studied in patients with severe hepatic impairment."

The above-mentioned changes are acceptable. They are supported by results of study M01-347.

Yuanchao (Derek) Zhang, Ph.D.
Clinical Pharmacology and
Biopharmaceutics Reviewer, DPE III
Office of Clinical Pharmacology and
Biopharmaceutics

Concurrence:

Kellie S. Reynolds, Pharm. D.
Clinical Pharmacology and
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Individual Clinical Pharmacology Reports (1)

M01-347

TITLE: Evaluation of the multiple dose pharmacokinetics of lopinavir/ritonavir in HIV infected subjects with mild and moderate hepatic insufficiency

BACKGROUND: The sponsor provided the study report to fulfill a phase IV commitment (#9). Specifically, this commitment requested the evaluation of Kaletra pharmacokinetics in subjects with mild and moderate hepatic impairment, to allow for the determination of dosing recommendations.

OBJECTIVES: To assess the effect of mild and moderate hepatic impairment on the pharmacokinetics of lopinavir/ritonavir after multiple dosing in HIV-infected subjects

SUBJECTS AND STUDY DESIGN: This was a phase 1, open-label, multicenter study. A total of 24 subjects were enrolled in the study, 12 HIV-infected control subjects with no evidence of hepatic dysfunction and 12 HIV-infected subjects with hepatic impairment (six mild and six moderate by Child-Pugh scores, 5-6 and 7-9, respectively). The study consisted of one 14-day period. On Study Days 1 through 14, all subjects received lopinavir 400 mg/ritonavir 100 mg BID. The study drugs were administered within 30 minutes after a meal.

FORMULATION: Kaletra soft gelatin capsules of lopinavir 133.3mg/ritonavir 33.3 mg strength

PHARMACOKINETIC SAMPLE COLLECTION: On Study Day 14, blood samples were collected prior to dosing (0 hour) and at 1, 2, 4, 6, 8, 10, and 12 hours after dosing. In addition, a 5-mL sample was collected prior to dosing (0 hour) and 6 hours after dosing for lopinavir protein binding measurement on Study Day 14. On Study Day 7 and one day between Study Days 10 and 12, trough blood samples were collected immediately prior to dosing in the morning.

PHARMACOKINETIC DATA ANALYSIS: Values for the pharmacokinetic parameters of lopinavir and ritonavir, including C_{max}, T_{max}, AUC_{0-12} and C_{trough}, were calculated using noncompartmental methods. Oral clearance was calculated based on AUC_{0-12}. The lopinavir and ritonavir PK variables and lopinavir protein binding percentage were examined by analysis of covariance (ANCOVA) with a classification by the three hepatic function groups. The mild and moderate hepatic impairment groups were compared to the normal hepatic function group by a test with a significance level of 0.05.

PHARMACOKINETIC RESULTS: Mild and moderate hepatic impairment had a similar effect on lopinavir pharmacokinetics. When data from the mild and moderate hepatic impairment groups were combined, hepatic impairment resulted in a 30% increase in total lopinavir AUC_{12}, 20% increase in C_{max} and 80% increase in C_{min}. The percent of unbound lopinavir was similar between mild and moderate hepatic impairment groups, but higher than that in the control group. After accounting for the differences in lopinavir protein binding, hepatic impairment increased unbound lopinavir $AUC_{u,12}$ by 68%, $C_{u,max}$ by 56% and $C_{u,min}$ by 130%.

Hepatic impairment increased low dose ritonavir AUC_{12} by 181%, C_{max} by 221% and C_{min} by 208% in moderate hepatic impairment group, and increased AUC_{12} by 39%, C_{max} by 60% and C_{min} by 52% in mild hepatic impairment group.

Table 1. Mean ± SD Pharmacokinetic Parameters of Lopinavir on Study Day 14

	Mild Hepatic Impairment (N=6)	Moderate Hepatic Impairment (N=6)	Mild +Moderate Hepatic Impairment (N=12)	Normal (N=12)
T_{max} (h)	3.0 ± 1.7[a]	4.3 ± 0.8	3.7 ± 1.4	5.0 ± 1.8
C_{max} (µg/mL)	12.22 ± 6.57	10.48 ± 3.39	11.35 ± 5.07	9.11 ± 2.94
C_{trough} (µg/mL)	8.71 ± 4.31[a]	7.81 ± 3.24[b]	8.26 ± 3.66[b]	5.19 ± 2.46
C_{min} (µg/mL)	6.33 ± 3.92[b]	5.81 ± 1.84[a]	6.07 ± 2.93[a]	3.84 ± 2.16
AUC_{12} (µg-h/mL)	109.5 ± 55.1	91.5 ± 24.1	100.5 ± 41.6	77.7 ± 30.3
CL/F (L/h)	4.5 ± 2.3	4.6 ± 1.2	4.5 ± 1.7	5.9 ± 2.3
$T_{1/2}$[c] (h)	9.6 ± 2.0	12.5 ± 4.6	10.8 ± 3.2	5.8 ± 2.7

a: Statistically significantly different from control (ANCOVA, $p<0.05$)
b: Marginally statistically significantly different from control (ANCOVA, $0.05<p<0.10$)
c: Harmonic mean and pseudo-standard deviation

Table 2. Mean ± SD Pharmacokinetic Parameters of Ritonavir on Study Day 14

	Mild Hepatic Impairment (N=6)	Moderate Hepatic Impairment (N=6)	Normal (N=12)
T_{max} (h)	3.3 ± 1.6[a]	4.3 ± 0.8	5.3 ± 1.6
C_{max} (µg/mL)	1.35 ± 1.24[b]	2.18 ± 0.63[a]	0.71 ± 0.27
C_{trough} (µg/mL)	0.51 ± 0.38[b]	0.93 ± 0.39[a]	0.28 ± 0.17
C_{min} (µg/mL)	0.24 ± 0.19	0.44 ± 0.22[b]	0.15 ± 0.08
AUC_{12} (µg-h/mL)	7.15 ± 5.12	12.56 ± 2.49[a]	4.76 ± 1.91
CL/F (L/h)	18.3 ± 8.3	8.3 ± 1.8	25.2 ± 13.4
$T_{1/2}$[c] (h)	3.6 ± 0.6	4.3 ± 1.5	3.5 ± 1.3

a: Statistically significantly different from control (ANCOVA, $p<0.05$)
b: Marginally statistically significantly different from control (ANCOVA, $0.05<p<0.10$)
c: Harmonic mean and pseudo-standard deviation

Table 3. Mean ± SD Protein Binding of Lopinavir on Study Day 14

	% Unbound 0 hour	% Unbound 6 hour	% Unbound Average
Control	0.74 ± 0.08	0.64 ± 0.08	0.69 ± 0.06
Mild	1.02 ± 0.40	0.76 ± 0.12	0.89 ± 0.21
Moderate	1.02 ± 0.10	0.86 ± 0.15	0.94 ± 0.10
Mild + Moderate	1.02 ± 0.28	0.81 ± 0.14	0.91 ± 0.16

Table 4. Mean ± SD Pharmacokinetic Parameters of Unbound Lopinavir on Study Day 14

	Mild Hepatic Impairment (N=6)	Moderate Hepatic Impairment (N=6)	Mild +Moderate Hepatic Impairment (N=12)	Normal (N=12)
$C_{u,max}$ (µg/mL)	0.10 ± 0.04[a]	0.10 ± 0.03[a]	0.10 ± 0.03[a]	0.06 ± 0.02
$C_{u,trough}$ (µg/mL)	0.07 ± 0.03[a]	0.07 ± 0.03[a]	0.07 ± 0.03[a]	0.04 ± 0.02
$C_{u,min}$ (µg/mL)	0.05 ± 0.03[a]	0.05 ± 0.01[a]	0.05 ± 0.02[a]	0.03 ± 0.01
$AUC_{u,12}$ (µg-h/mL)	0.92 ± 0.36[a]	0.85 ± 0.19[a]	0.89 ± 0.28[a]	0.53 ± 0.21
CL_u/F (L/h)	498 ± 213	498 ± 153	498 ± 176	857 ± 327

a: Statistically significantly different from control (ANCOVA, $p<0.05$)

Table 5. Lopinavir and Ritonavir Point Estimates (Hepatic Impairment Group vs. Control, 90% Confidence Intervals)

	AUC_{12}	C_{max}	C_{min}
		Total Lopinavir	
Mild	1.367 (0.972 – 1.923)	1.254 (0.911 – 1.726)	1.710 (1.066 – 2.743)
Moderate	1.229 (0.874 – 1.729)	1.155 (0.839 – 1.589)	1.870 (1.159 – 3.016)
Mild + Moderate	1.296 (0.987 – 1.703)	1.203 (0.932 – 1.553)	1.787 (1.224 – 2.608)
		Unbound Lopinavir	
Mild	1.702 (1.242 – 2.331)	1.561 (1.170 – 2.083)	2.128 (1.354 – 3.345)
Moderate	1.658 (1.210 – 2.272)	1.558 (1.168 – 2.078)	2.491 (1.576 – 3.936)
Mild + Moderate	1.680 (1.307 – 2.158)	1.559 (1.239 – 1.962)	2.299 (1.598 – 3.307)
		Total Ritonavir	
Mild	1.392 (0.956 – 2.028)	1.605 (1.055 – 2.443)	1.520 (0.937 – 2.464)
Moderate	2.812 (1.931 – 4.096)	3.209 (2.108 – 4.884)	3.078 (1.898 – 4.992)

Figure 1. Mean (SD) Lopinavir Plasma Concentration-Time Profiles on Study Day 14

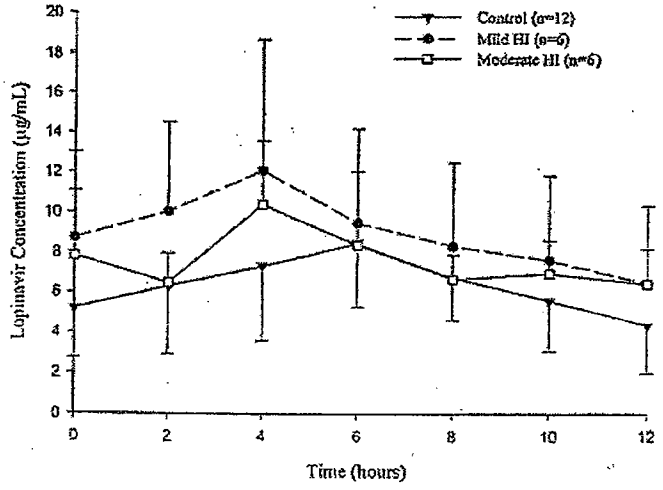


Figure 2. Mean (SD) Ritonavir Plasma Concentration-Time Profiles on Study Day 14

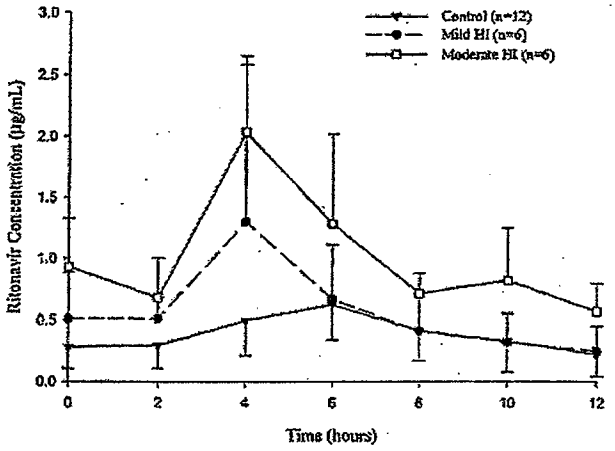


Figure 3. Lopinavir and Ritonavir AUC_{12} on Study Day 14, Individual and Mean (SD)

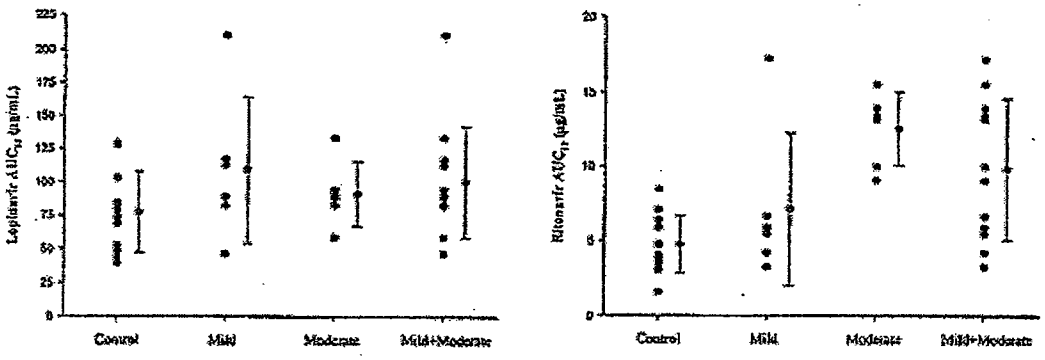


Figure 4. Lopinavir and Ritonavir C_{max} on Study Day 14, Individual and Mean (SD)

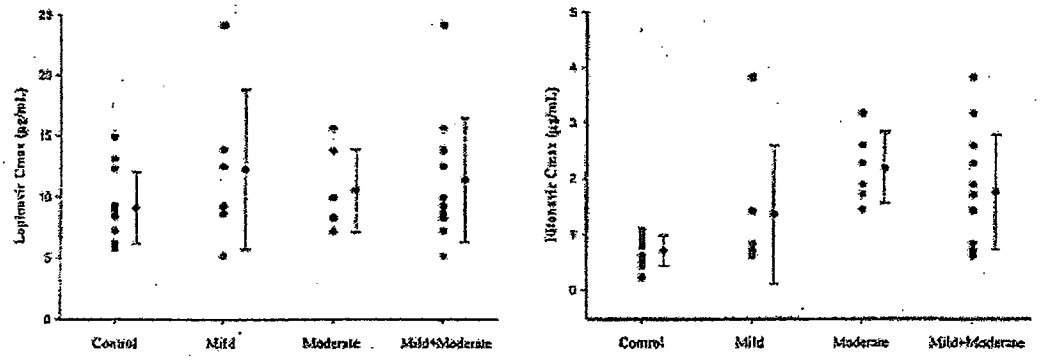


Figure 5. Lopinavir and Ritonavir C_{min} on Study Day 14, Individual and Mean (SD)

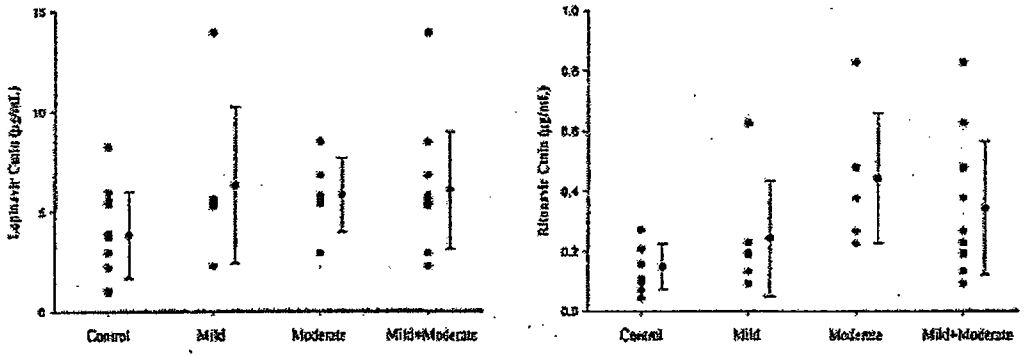


Figure 6. Mean (SD) Lopinavir Trough Concentrations

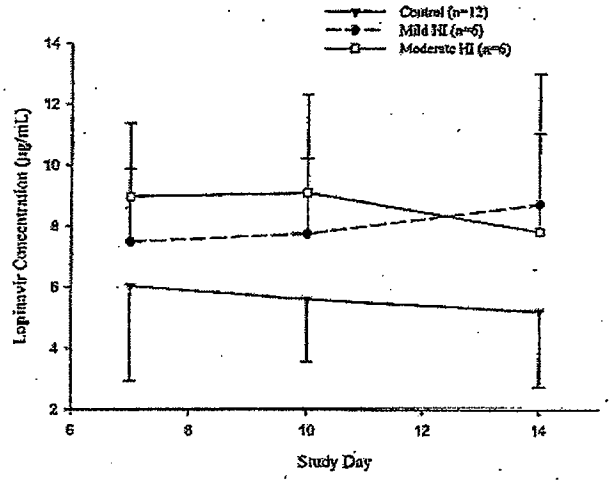
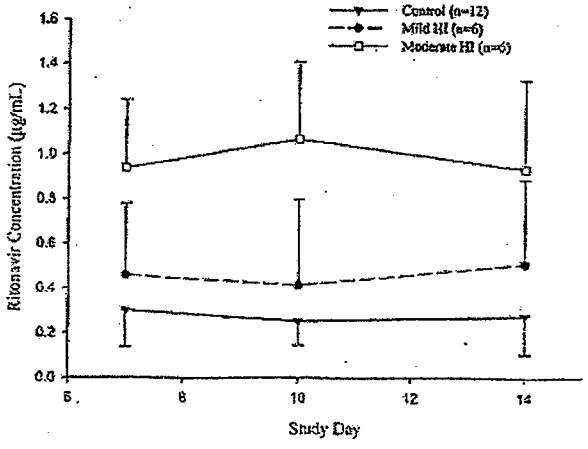


Figure 7. Mean (SD) Ritonavir Trough Concentrations



CONCLUSIONS AND DISCUSSION: Both lopinavir and ritonavir are extensively metabolized by CYP3A. It was expected that clearance of lopinavir and ritonavir might be lower in hepatically impaired subjects. This study demonstrated that mild and moderate hepatic impairment had a similar effect on lopinavir pharmacokinetics. When data from the mild and moderate hepatic impairment groups were combined, hepatic impairment resulted in a 30% increase in total lopinavir AUC_{12}, 20% increase in C_{max} and 80% increase in C_{min}. Hepatic impairment increased low dose ritonavir AUC_{12} by 181%, C_{max} by 221% and C_{min} by 208% in moderate hepatic impairment group, and increased AUC_{12} by 39%, C_{max} by 60% and C_{min} by 52% in mild hepatic impairment group.

The Sponsor indicated that one subject, a 35-year-old white female with a body weight of 49 kg, showed an almost doubled exposure of both lopinavir and ritonavir compared to the other five mild hepatically impaired subjects (Figures 3-5), leading to a large inter-subject variability for the mild hepatic impairment group. Without this subject, the five remaining mild hepatically impaired subjects showed similar lopinavir and ritonavir exposures compared to the control group. The Sponsor examined this case and nothing was abnormal for this subject. No clear reason was identified.

There were no adverse events or trends in laboratory values that were of clinical concern during the 14-day study period. Based on these pharmacokinetic and safety observations, there appears to be no need to decrease the dose of Kaletra in mild and moderate hepatically impaired subjects.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-014
21-251 / S-010

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

EXCLUSIVITY SUMMARY FOR NDA #21-226/21-251 SUPPL # 014/010

Trade Name: Kaletra Generic Name: Lopinavir/Ritonavir

Applicant Name Abbott HFD # 530

Approval Date If Known October 19, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE-8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce

an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-226 _____

NDA# 21-251 _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This

section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies

relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

M97-720 and M97-265

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously

approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /__X_/ NO /___/

Investigation #2 YES /__X_/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

21-226(Capsules) _____

21-251(Oral soln) _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /__X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in

#2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____YES /_X__/ ! NO /___/ Explain: _____

Investigation #2 !

IND # _____YES /_X__/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

Signature Vasavi Reddy Date 10/19/04
Title: REGULATORY PROJECT MANAGER

Signature of Office/ Division Director
JEFF MURRAY, M.D., MPH
DEPUTY DIV DIRECTOR

Date 10/19/04

Form OGD-011347 Revised 05/10/2004

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-226/21-251 Supplement Type (e.g. SE5): SE-8 Supplement Number: 014 /010

Stamp Date: December 19, 2003 Action Date: October 19, 2004

HFD 530 Trade and generic names/dosage form: Kaletra (Lopinavir/Ritonavir)

Applicant: Abbott Therapeutic Class: Anti-Retroviral Drug

Indication(s) previously approved: Treatment for HIV-1 infection in combination with other antiretroviral agents

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of HIV-1 infection in combination with other antiretroviral agents.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☒ No: Please check all that apply: ___Partial Waiver __X__Deferred ___Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.** neonates **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 16 **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other: Studies are ongoing

Date studies are due (mm/dd/yy): _____

...udies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.** ≥6months **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-226/S-014**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-226
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

Certification Requirement
For Approval of a Drug Product
Concerning Using Services of Debarred Persons

- DEBARMENT STATEMENT -

Any application for approval of a new drug product submitted on or after June 1, 1992, per FD&C Act Section 306 (k)(1), must include:

> (1) A certification that the applicant did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with such application.

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with such application.

[Generic Drug Enforcement Act of 1992, Section 306(k)(1) of 21 USC 335a(k)(1)].

Greg Bosco

Greg Bosco
Assoc. Director, PPD Regulatory Affairs
Abbott Laboratories

12/15/03
Date