CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-226 / S-006
21-251 / S-005

Trade Name: Kaletra

Generic Name: (lopinavir / ritonavir)

Sponsor: Abbott Laboratories

Approval Date: November 27, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-006
21-251 / S-005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-006
21-251 / S-005

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-226 /S-006
NDA 21-251 /S-005

Abbott Laboratories
Attention: Greg Bosco
Associate Director, PPD Regulatory Affairs
D-491/AP6B-1SW
100 Abbott Park Road
Abbott Park, IL 60064-6108

Dear Mr. Bosco:

Please refer to your supplemental new drug applications dated January 30, 2002, received January 31, 2002 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KALETRA® (lopinavir/ritonavir) Capsules and KALETRA® (lopinavir/ritonavir) Oral Solution.

We acknowledge receipt of your submissions dated:

October 4, 2002	November 15, 2002
October 10, 2002	November 20, 2002
November 7, 2002	November 26, 2002

These supplemental new drug applications contain 48-week safety and efficacy data (updated from 24-week data) from Study M98-888 included in the original NDA. These supplements provide for the use of KALETRA Capsules and KALETRA Oral Solution in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of KALETRA of 48 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 72 weeks duration.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the 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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 21-226 /S-006, NDA 21-251 /S-005." Approval of these submissions by FDA is not required before the labeling is used.

We approved these NDAs under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 314.510.

We also remind you of your outstanding post-marketing study commitments outlined in the original accelerated approval letter dated September 15, 2000 and the approval letter for supplements 003 and 004 dated January 18, 2002. We will address the status of those commitments already submitted for review in a separate correspondence.

The text in italics below addresses the application of FDA's Pediatric Rule at [21 CFR 314.55/21 CFR 601.27] to this [NDA/BLA]. The Pediatric Rule has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. The government has not yet decided whether to seek a stay of the court's order. In addition, the government has not yet decided whether to appeal the decision; an appeal must be filed within 60 days. **Therefore, this letter contains a description of the pediatric studies that would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal.** Please be aware that whether or not these pediatric studies will be required will depend upon the resolution of the litigation. FDA will notify you as soon as possible as to whether this application will be subject to the requirements of the Pediatric Rule as described below. In any event, we hope you will decide to conduct these pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on information submitted, we conclude the following:

For the treatment of HIV-1,

- *We are deferring submission of pediatric studies for patients ages <1 month to 6 months and ages 12 years to 16 years until July 1, 2004.*
- *You have fulfilled the pediatric study requirement at this time for patients ages 6 months to 12 years.*

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

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, HF-2
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 Sean J. Belouin, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

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

/s/

Debra Birnkrant
11/27/02 11:11:25 AM
NDA 21-226, NDA 21-251

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-006
21-251 / S-005

LABELING

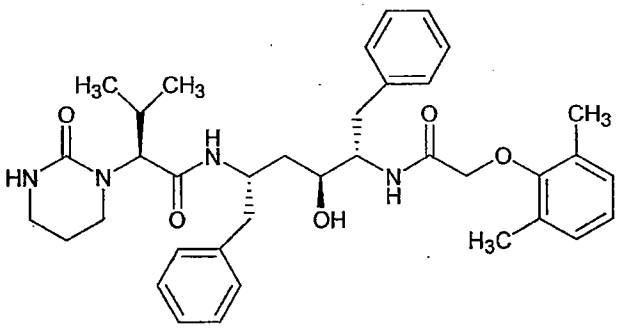
(Nos. 3956 and 3959)
NEW

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

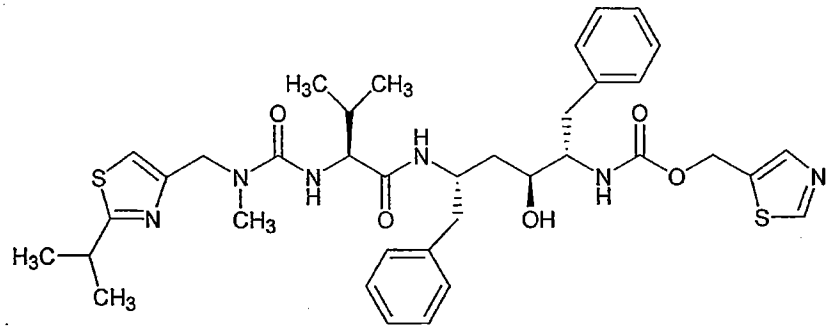
R_x only
Tear at perforation to dispense patient information.

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

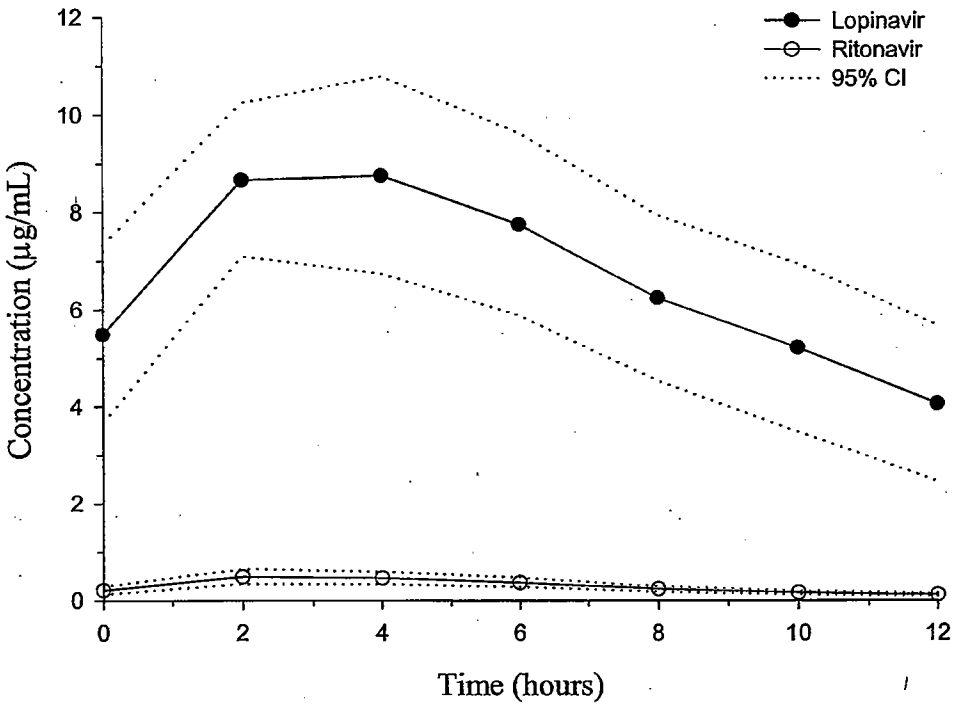
There are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. Further studies are needed to assess the association between specific mutational patterns and virologic response rates.

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 for 3-4 weeks from a pharmacokinetic study in HIV-infected adult subjects (n=21).

Figure 1:
Mean Steady-State Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-Infected Adult Subjects (N = 21)



Absorption: In a pharmacokinetic study in HIV-positive subjects (n=21) without meal restrictions, multiple dosing with 400/100 mg KALETRA BID for 3 to 4 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.6 ± 4.4 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 5.5 ± 4.0 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 82.8 ± 44.5 µg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA liquid relative to the capsule formulation.

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 half-life of lopinavir over a 12 hour dosing interval averaged 5-6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 L/h.

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. Although KALETRA has not been studied in patients with hepatic impairment, lopinavir concentrations may be increased in these patients (see **PRECAUTIONS**).

Drug-Drug Interactions: See also **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS: Drug Interactions**.

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations

of the other drug, which could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS**).

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit 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 (with/without co-administered drug) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir[1]	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	0.89 (0.83, 0.95)	0.85 (0.81, 0.90)	0.81 (0.74, 0.89)
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[2]	600 QHS, 9 d	400/100 BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
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)
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)

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

1 Composite effect of amprenavir 450 and 750 mg Q12h regimens on lopinavir pharmacokinetics.

2 The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

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

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

Table 3: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA
(See Precautions, Table 9 for Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (with/without KALETRA) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir	450 BID, 5 d 750 BID, 5 d	400/100 BID, 22 d	12 10	See text below for discussion of interaction.		
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)
Efavirenz	600 QHS, 9 d	400/100 BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum®)	400/100 BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Indinavir	600 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		
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
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 25-*O*-desacetyl rifabutin Rifabutin + 25-*O*-desacetyl rifabutin[1]	300 QD, 10 d; 150 QD, 10 d	400/100 BID, 10 d	12	2.12 (1.89, 2.38) 23.6 (13.7, 25.3) 3.46 (3.07, 3.91)	3.03 (2.79, 3.30) 47.5 (29.3, 51.8) 5.73 (5.08, 6.46)	4.90 (3.18, 5.76) 94.9 (74.0, 122) 9.53 (7.56, 12.01)
Saquinavir	800 single dose	400/100 BID, 10 d	11	See text below for discussion of interaction.		

All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.
[1] Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.
* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.
N/A =not available.

Effect of KALETRA on other Protease Inhibitors (PIs): The pharmacokinetics of single-dose indinavir and saquinavir, and multiple-dose amprenavir obtained in healthy subjects after at least 10 days of KALETRA 400/100 mg BID were compared to historical data in HIV-infected subjects (refer to Table 3 for information on study design and doses). Because of the limitations in the study design and the use of comparisons between healthy and HIV infected subjects, it is not possible to recommend definitive dosing recommendations. However, based on these comparisons, amprenavir 750 mg BID and indinavir 600 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC, lower C_{max}, and higher C_{min} compared to their respective established clinical dosing regimens. Saquinavir 800 mg BID, when co-administered with KALETRA 400/100 mg BID, may produce a similar AUC and higher C_{min} to its respective established clinical dosing regimen (no comparative information regarding C_{max}). The clinical significance of the lower C_{max} and higher C_{min} is unknown. Appropriate doses of amprenavir, indinavir and saquinavir in combination with KALETRA with respect to safety and efficacy have not been established (see **PRECAUTIONS** – Table 9).

INDICATIONS AND USAGE

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

Description of Clinical Studies

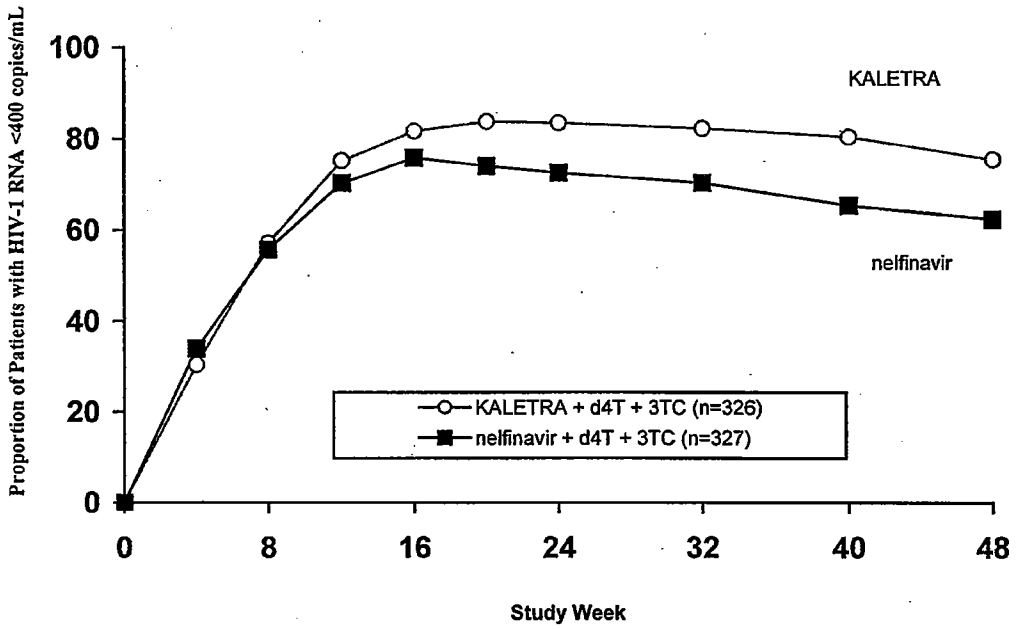
Patients Without Prior Antiretroviral Therapy

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

Study 863 is an ongoing, randomized, double-blind, multicenter trial comparing treatment with KALETRA (400/100 mg BID) plus stavudine and lamivudine versus nelfinavir (750 mg TID) plus stavudine and lamivudine in 653 antiretroviral treatment naive patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline CD4 cell count was 259 cells/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 FIGURE 2 AND TABLE 4, RESPECTIVELY.

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



* Roche AMPLICOR HIV-1 MONITOR Assay.

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

Table 4: Outcomes of Randomized Treatment Through Week 48 (Study 863)

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

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

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV RNA <400 copies/mL (75%

vs. 62%, respectively) and HIV RNA <50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV RNA level subgroups is presented in Table 5.

TABLE 5: PROPORTION OF RESPONDERS THROUGH WEEK 48 BY BASELINE VIRAL LOAD (STUDY 863)

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

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

Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was 207 cells/mm^3 for the KALETRA arm and 195 cells/mm^3 for the nelfinavir arm.

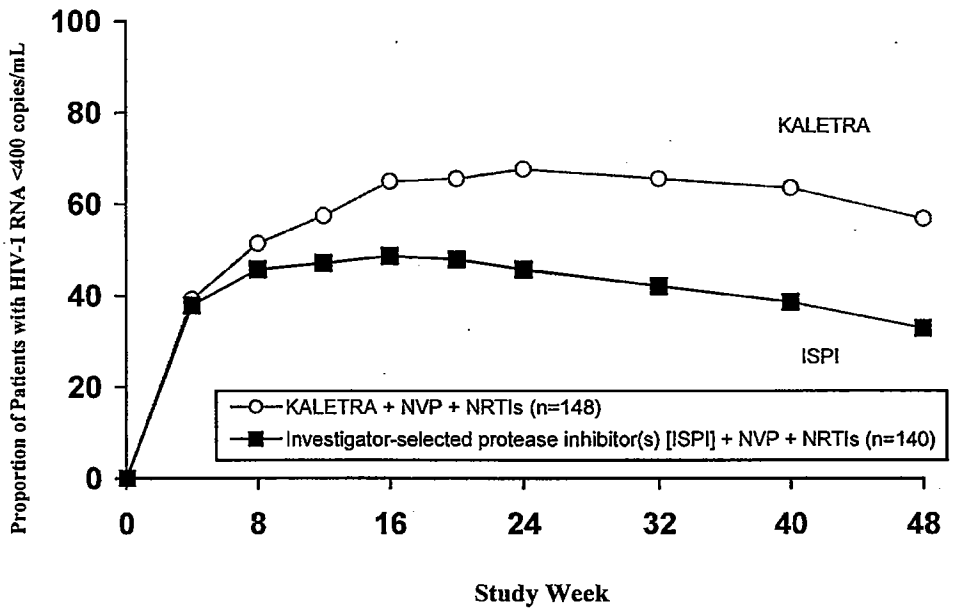
Patients with Prior Antiretroviral Therapy

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 CD4 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 FIGURE 3 AND TABLE 6, RESPECTIVELY.

FIGURE 3: VIROLOGIC RESPONSE THROUGH WEEK 48, STUDY 888*†



* Roche AMPLICOR HIV-1 MONITOR Assay.

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

Table 6. Outcomes of Randomized Treatment Through Week 48 (Study 888)

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

* Corresponds to rates at Week 48 in Figure 3.

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

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

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

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

Through 48 weeks of therapy, the mean increase from baseline in CD4 cell count was 111 cells/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). Patients in study 720 had a mean age of 35 years, 70% were Caucasian, and 96% were male, while patients in study 765 had a mean age of 40 years, 73% were Caucasian, and 90% were male. Mean (range) baseline CD4 cell counts for patients in study 720 and study 765 were 338 (3-918) and 372 (72-807) cells/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 72 weeks of treatment, for patients randomized to the 400/100 mg BID dose of KALETRA, the proportion of patients with plasma HIV-1 RNA <400 (<50) copies/mL was 80% (78%) in study 720 [n=51] and 75% (58%) in study 765 [n=36]. The corresponding mean increase in CD4 cell count was 256 cells/mm^3 for study 720 and 174 cells/mm^3 for study 765. At 72 weeks, 13 patients (13%) had discontinued study 720 for any reason, including four discontinuations (4%) secondary to adverse events or laboratory abnormalities with one of these discontinuations (1%) being attributed to a KALETRA adverse event. In study 765, 13 patients (19%) had discontinued the study for any reason at 72 weeks, including six discontinuations (9%) secondary to adverse events or laboratory abnormalities with three of these discontinuations (4%) being attributed to KALETRA adverse events.

CONTRAINDICATIONS

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

Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A or CYP2D6 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
Antiarrhythmics	Flecainide, Propafenone
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 or CYP2D6 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics: Drug-Drug Interactions, CONTRAINDICATIONS – Table 7: Drugs That Are Contraindicated With KALETRA, PRECAUTIONS - Table 8: Drugs That Should Not Be Co-administered With KALETRA** and **Table 9: Established and Other Potentially Significant Drug Interactions**).

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

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

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

Pancreatitis

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

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

Diabetes Mellitus/Hyperglycemia

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

PRECAUTIONS

Hepatic Impairment and Toxicity

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring

should be considered in these patients, especially during the first several months of KALETRA treatment.

Resistance/Cross-resistance

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

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

Fat Redistribution

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

Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS** – Table 11). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **PRECAUTIONS Table 9: Established and Other Potentially Significant Drug Interactions** for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

Information for Patients

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

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

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

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

PATIENTS TAKING DIDANOSINE SHOULD TAKE DIDANOSINE ONE HOUR BEFORE OR TWO HOURS AFTER KALETRA.

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

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

KALETRA should be taken with food to enhance absorption.

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

Drug Interactions

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **Table 9: Established and Other Potentially Significant Drug Interactions**). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (>3-fold) when co-administered with KALETRA.

KALETRA inhibits CYP2D6 *in vitro*, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit 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
Antiarrhythmics: flecainide, propafenone	CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias.
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.
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:	May lead to loss of virologic response and possible resistance to KALETRA

St. John's wort (hypericum perforatum)	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).
HIV-Protease Inhibitors: amprenavir*, indinavir*, saquinavir*	When co-administered with reduced doses of concomitant protease inhibitors: ↑ Amprenavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Indinavir (Similar AUC, ↓ C_{max}, ↑ C_{min}) ↑ Saquinavir (Similar AUC, ↑ C_{min})	Alterations in concentrations (e.g., AUC, C_{max} and C_{min}) are noted when reduced doses of concomitant protease inhibitors are co-administered with KALETRA. Appropriate doses of the combination with respect to safety and efficacy have not been established (see **CLINICAL PHARMACOLOGY**: Table 3 and Effect of KALETRA on other Protease Inhibitors (PIs)).
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	↑ Ketoconazole ↑ Itraconazole	High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antimycobacterial: rifabutin*	↑ Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
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).
Erectile Dysfunction Agent: sildenafil	↑ Sildenafil	Use with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitors: atorvastatin*	↑ Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
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	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and KALETRA are co-administered.

* See **CLINICAL PHARMACOLGY** for Magnitude of Interaction, Tables 2 and 3

Other Drugs:
Drug interaction studies reveal no clinically significant interaction between KALETRA and 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
Long-term carcinogenicity studies of KALETRA in animal systems have not been completed.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA BID). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA BID regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

LOPINAVIR IN COMBINATION WITH RITONAVIR AT A 2:1 RATIO PRODUCED NO EFFECTS ON FERTILITY IN MALE AND FEMALE RATS AT LEVELS OF 10/5, 30/15 OR 100/50 MG/KG/DAY. BASED ON AUC MEASUREMENTS, THE EXPOSURES IN RATS AT THE HIGH DOSES WERE APPROXIMATELY 0.7-FOLD FOR LOPINAVIR AND 1.8-FOLD FOR RITONAVIR OF THE EXPOSURES IN HUMANS AT THE RECOMMENDED THERAPEUTIC DOSE (400/100 MG BID).

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

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving KALETRA.**

Geriatric Use

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

Pediatric Use

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

Study 940 is an ongoing open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naive (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per 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 CD4 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 CD4 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 72 weeks (Phase I/II) are presented in Table 10. For other information regarding observed or potentially serious adverse events, please see **WARNINGS** and **PRECAUTIONS**.

Table 10: Percentage of Patients with Selected Treatment-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 (72 Weeks)	Study 957[3] and Study 765[4] (48-72 Weeks)

	KALETRA 400/100 mg BID + d4T + 3TC (N=326)	Nelfinavir 750 mg TID + d4T + 3TC (N=327)	KALETRA 400/100 mg BID + NVP + NRTIs (N=148)	Investigator-selected protease inhibitor(s) + NVP + NRTIs (N=140)	KALETRA BID[2] + d4T + 3TC (N= 84)	KALETRA BID + NNRTI + NRTIs (N= 127)
Body as a Whole						
Abdominal Pain	4%	3%	2%	2%	5%	2%
Asthenia	4%	3%	3%	6%	7%	8%
Chills	0%	<1%	2%	0%	1%	0%
Fever	<1%	<1%	2%	1%	0%	2%
Headache	2%	2%	2%	3%	7%	2%
Digestive System						
Anorexia	1%	<1%	1%	3%	0%	0%
Diarrhea	16%	17%	7%	9%	24%	18%
Dyspepsia	2%	<1%	1%	1%	1%	0%
Dysphagia	0%	0%	2%	1%	1%	0%
Flatulence	2%	1%	1%	2%	1%	2%
Nausea	7%	5%	7%	16%	15%	4%
Vomiting	2%	2%	4%	12%	5%	2%
Nervous System						
Depression	1%	2%	1%	2%	0%	2%
Insomnia	2%	1%	0%	2%	2%	2%
Skin and Appendages						
Rash	1%	2%	2%	1%	4%	2%

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

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

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

4 Includes adverse event data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 72 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.

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

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

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

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

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

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

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

Musculoskeletal System: Arthralgia, arthrosis and myalgia.

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

Respiratory System: Asthma, bronchitis, dyspnea, lung edema, pharyngitis, rhinitis, and sinusitis.

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

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

Urogenital System: Abnormal ejaculation, gynecomastia, hypogonadism male, kidney calculus, and urine abnormality.

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

Body as a whole: Redistribution/accumulation of body fat has been reported (see **PRECAUTIONS, Fat Redistribution**).

Cardiovascular: Bradyarrhythmias.

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

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

Table 11: Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Patients

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

1 ULN = upper limit of the normal range; N/A = Not Applicable.
2 Includes clinical laboratory data from dose group I (400/100 mg BID only [N=16]) and dose group II (400/100 mg BID [N=35] and 400/200 mg BID [N=33]).
3 Includes clinical laboratory data from patients receiving 400/100 mg BID (n=29) or 533/133 mg BID (n=28) for 48 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.
4 Includes clinical laboratory data from patients receiving 400/100 mg BID (n=36) or 400/200 mg BID (n=34) for 72 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.

Pediatrics:

Treatment-Emergent Adverse Events: KALETRA has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse event profile seen during a clinical trial was similar to that for adult patients.

Taste aversion, vomiting, and diarrhea were the most commonly reported drug related adverse events of any severity in pediatric patients treated with combination therapy including KALETRA for up to 48 weeks in Study 940. A total of 8 children experienced moderate or severe adverse events at least possibly related to KALETRA. Rash (reported in 3%) was the only drug-related clinical adverse event of moderate to severe intensity observed in ≥ 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	3.0%
TOTAL BILIRUBIN	≥ 3.0 X ULN	3.0%
SGOT/AST	> 180 U/L	8.0%
SGPT/ALT	> 215 U/L	7.0%
TOTAL CHOLESTEROL	> 300 MG/DL	3.0%
AMYLASE	> 2.5 X ULN	7.0%[2]
CHEMISTRY	LOW	
SODIUM	< 130 MEQ/L	3.0%
HEMATOLOGY	LOW	
PLATELET COUNT	< 50 X 10^9/L	4.0%
NEUTROPHILS	< 0.40 X 10^9/L	2.0%

[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 or nevirapine: 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 **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	Dose (mg/kg)*	Volume of oral solution BID

(kg)		(80 mg lopinavir/20 mg ritonavir per mL)
Without nevirapine or efavirenz		
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 or nevirapine: 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. The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz or nevirapine 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 or efavirenz		
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)
Packages of 120 unit dose blisters.....(**NDC** 0074-3959-11)

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.

What is KALETRA and how does it work?

KALETRA is a combination of two medicines. They are lopinavir and ritonavir. KALETRA is a type of medicine called an HIV (human immunodeficiency virus) protease (PRO-tee-ase) inhibitor. KALETRA is always used in combination with other anti-HIV medicines to treat people with human immunodeficiency virus (HIV) infection. KALETRA is for adults and for children age 6 months and older.

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

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

Does KALETRA cure HIV or AIDS?

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

Does KALETRA reduce the risk of passing HIV to others?

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

How should I take KALETRA?

- You should stay under a doctor's care when taking KALETRA. Do not change your treatment or stop treatment without first talking with your doctor.

- You must take KALETRA every day exactly as your doctor prescribed it. The dose of KALETRA may be different for you than for other patients. Follow the directions from your doctor, exactly as written on the label.

- Dosing in adults (including children 12 years of age and older):
  The usual dose for adults is 3 capsules (400/100 mg) or 5.0 mL of the oral solution twice a day (morning and night), in combination with other anti-HIV medicines.

- Dosing in children from 6 months to 12 years of age:
  Children from 6 months to 12 years of age can also take KALETRA. The child's doctor will decide the right dose based on the child's weight.

- Take KALETRA with food to help it work better.

- Do not change your dose or stop taking KALETRA without first talking with your doctor.

- When your KALETRA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to KALETRA and become harder to treat.

- Be sure to set up a schedule and follow it carefully.

- Only take medicine that has been prescribed specifically for you. Do not give KALETRA to others or take medicine prescribed for someone else.

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

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

What happens if I take too much KALETRA?

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

As with all prescription medicines, KALETRA should be kept out of the reach of young children. KALETRA liquid contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of KALETRA, it could make him/her sick from too much alcohol. Contact your local poison control center or emergency room immediately if this happens.

Who should not take KALETRA?

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

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

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

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

Can I take KALETRA with other medications?*

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

MEDICINES YOU SHOULD NOT TAKE WITH KALETRA:

- Do not take the following medicines with KALETRA because they can cause serious problems or death if taken with KALETRA.

- Dihydroergotamine, ergonovine, ergotamine and methylergonovine such as Cafergot®, Migranal®, D.H.E. 45®, Ergotrate Maleate, Methergine, and others
- Halcion® (triazolam)
- Hismanal® (astemizole)
- Orap® (pimozide)
- Propulsid® (cisapride)
- Rythmol® (propafenone)
- Seldane® (terfenadine)
- Tambocor™ (flecainide)
- Versed® (midazolam)

- Do not take KALETRA with rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®. Rifampin may lower the amount of KALETRA in your blood and make it less effective.

- Do not take KALETRA with St. John's wort (hypericum perforatum), an herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease KALETRA levels and lead to increased viral load and possible resistance to KALETRA or cross-resistance to other anti-HIV medicines.

- Do not take KALETRA with the cholesterol-lowering medicines Mevacor® (lovastatin) or Zocor® (simvastatin) because of possible serious reactions. There is also an increased risk of drug interactions between KALETRA and Lipitor® (atorvastatin); talk to your doctor before you take any of these cholesterol-reducing medicines with KALETRA.

Medicines that require dosage adjustments:

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

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

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

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

- 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-006
21-251 / S-005

MEDICAL REVIEW

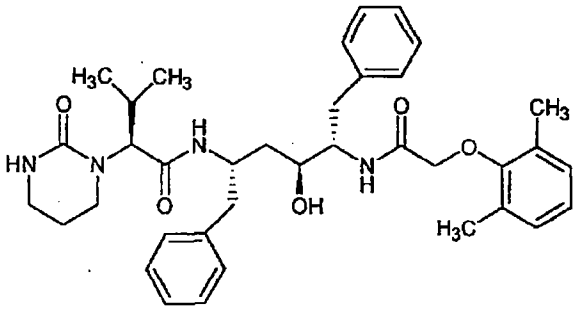
CLINICAL REVIEW

Medical Officer's Review

NDA 21-226, SE7-006
NDA 21-251, SE7-005

Date of submission:	January 30, 2002
Date received:	January 31, 2002
Draft review completed:	November 22, 2002
Final review completed:	December 3, 2002
Action date:	November 27, 2002
Reviewed by:	Linda L. Lewis, M.D. Medical Officer, HFD-530
Applicant:	Abbott Laboratories Pharmaceutical Products Division 100 Abbott Park Road D-491, AP30-1E Abbott Park, IL 60064-6157
Drug name:	Kaletra soft gel capsules Kaletra oral solution (ABT-378/ritonavir, lopinavir/ritonavir)
Formulation:	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)
Indication:	Treatment of HIV infection

Chemical structure:



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Clinical Review for NDA 21-226

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The results of Study M98-888 comparing lopinavir/ritonavir (Kaletra, ABT/378, LPV/RTV) to investigator-selected protease inhibitor (ISPI) in combination with two NRTIs (also investigator selected) and a newly prescribed NNRTI confirmed the efficacy of LPV/RTV in HIV-infected adults failing single PI-based therapy. LPV/RTV was shown to provide effective suppression of HIV replication in a greater proportion of patients than did the ISPI regimens through 48 weeks of dosing. Review of the safety data submitted with this supplement identified no new toxicity considered related to LPV/RTV and no new safety issues which require communication to practitioners and patients. This study extends the population confirmed to benefit from LPV/RTV since it has previously been shown to provide effective therapy in treatment naïve adults in a well controlled Phase 3 trial and in HIV-infected children > 6 months of age. Based on review of the clinical data provided, Traditional Approval should be granted to LPV/RTV.

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

No additional Phase 4 commitments were requested based on the review of this supplement. The sponsor was reminded of the outstanding Phase 4 commitments requested at the time of previous approval actions.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Lopinavir/ritonavir (Kaletra, ABT-378, LPV/RTV) is a co-formulation of two antiretroviral drugs in the class of HIV protease inhibitors (PIs). Lopinavir (LPV) serves as the active antiretroviral compound while ritonavir (RTV) serves, in this instance, 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 the basis of 24-week data showing declines in HIV-1 RNA levels and improvements in CD4 cell counts over the 24-

week study period. Original approval was granted September 15, 2000. Efficacy supplements containing 48-week data from an adult Phase III clinical trial (21-226, SE8-003) and the Phase 2 pediatric study (21-251, SE8-004) were completed in January, 2002, and the 48-week results were incorporated into the product label.

This submission includes 48-week data from a single trial of Kaletra in HIV-infected, PI-treatment experienced adults, Study M98-888. The dose of Kaletra evaluated in the study is the approved dose of [redacted]PV/100 mg RTV, given twice daily in combination with nevirapine (NVP) and two nucleoside reverse transcriptase inhibitors (NRTIs) compared to either single or dual investigator-selected protease inhibitor (ISPI) also in combination with NVP and two NRTIs. A total of 288 patients were randomized (148 to LPV/RTV and 140 to ISPI) and received at least one dose of study medication; 192 patients completed at least 48 weeks of study.

Summaries of the efficacy and safety data from Study M98-888 were incorporated into the product label.

B. Efficacy

In the recently published Guidance for Industry: Antiretroviral Drugs using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval, the Division proposed suppression of HIV replication over 48 weeks of drug dosing as an acceptable correlate of durable clinical benefit. The primary measure of efficacy in Study M98-888 was an HIV RNA PCR assay with lower limit of quantitation of 400 copies/ml. Study design and calculation of the primary endpoint, time to loss of virologic response to drug, were in accordance with the recommendations in the Guidance.

In this population, a greater proportion of patients receiving LPV/RTV achieved and maintained suppression of HIV RNA levels < 400 copies/ml through 48 weeks than did those who received ISPI regimens, 57% compared to 33%. A greater proportion of patients in the LPV/RTV group remained on study through the entire study period with more patients prematurely discontinuing in the ISPI arm due to adverse events, HIV-related events, and virologic failure. Both treatment groups achieved similar, significant decreases in mean log change from Baseline in HIV RNA and increases in mean CD4 cell counts over the 48 week study period.

These results are within the same range as those obtained in clinical trials of other PI-based antiretroviral regimens in treatment experienced patients. Durable response to treatment has generally been seen in smaller proportions of previously treated patients than in treatment naïve patients. The 57% response rate achieved in Study M98-888 can be compared to the response rate of 75% seen in treatment

naïve patients receiving LPV/RTV in Study M98-863 (reviewed in an earlier supplement).

C. **Safety**

All 288 patients who were randomized and received at least one dose of study medications were included in the safety analyses. The frequency and variety of clinical and laboratory evaluations was considered appropriate for the indication and patient population being studied. Average duration of follow-up was 372 days for patients receiving LPV/RTV and 335 days for patients receiving ISPI regimens.

In this population of HIV-infected adults, as in previously studied groups receiving LPV/RTV, the most commonly reported AEs were gastrointestinal events (anorexia, diarrhea, nausea, and vomiting) occurring in up to 45% of patients enrolled. These events have been associated with the use of LPV/RTV and other antiretroviral drugs and the proportions of patients reporting these events were similar to those presented in other studies. There were few identifiable differences between the treatment arms, with slightly more nausea and vomiting of moderate or severe intensity attributed to study drug in patients receiving ISPI regimens. Numerically more patients receiving LPV/RTV developed rashes (28%) and more LPV/RTV patients required dose interruption because of rash (7%), although all patients were receiving NVP. All six of the patients reporting "hepatitis" as an AE received ISPI regimens. Four of these patients had documented viral hepatitis and only 2 were thought to have drug related hepatitis or hepatic toxicity. Events fitting the description of body fat composition changes appeared to be evenly distributed across both treatment arms, occurring in about 8% of patients receiving LPV/RTV or ISPI. Similarly, AEs identified as HIV-related conditions, serious AEs, and deaths were balanced across the treatment arms.

The major laboratory toxicities associated with LPV/RTV use in Study M98-888 were hypercholesterolemia and hypertryglyceridemia occurring in 20% and 25% of LPV/RTV patients and similar proportions of ISPI patients. This phenomenon has been observed with many of the PIs and was noted during the original NDA review of LPV/RTV. Most of these events were managed medically and did not require premature discontinuation. Other laboratory findings such as elevated amylase, elevated SGOT or SGPT, and hyperglycemia were identified in numerically more patients receiving ISPI regimens. These abnormalities were documented in 1-6% of patients receiving LPV/RTV.

Although an extensive review of EKG data and cardiac events was undertaken during this review cycle, little objective evidence of a causal relationship between LPV/RTV use and cardiac arrhythmias was found. Findings of prolonged QTc intervals were identified in 18 patients, evenly distributed between the treatment

arms, without evidence of clinical consequences. Review of the post-marketing safety databases available revealed a few cases of serious arrhythmias that appeared to be significantly associated with LPV/RTV use.

The safety profile of LPV/RTV in this population of PI-treatment experienced patients was similar to that identified in other clinical trials of LPV/RTV. Not surprisingly, the rates of adverse events and laboratory abnormalities were slightly higher in this study population than in the population of treatment naïve patients enrolled in Study M98-863. After review and internal discussion it was decided that the events of bradyarrhythmias warranted inclusion in the product label in the section related to Post-marketing Experience. Otherwise, no new toxicity was considered related to LPV/RTV and no new safety issues requiring communication to practitioners and patients were identified.

D. Dosing

The approved dose of LPV/RTV in adults is 400 mg LPV/100 mg RTV taken twice daily. After review of the additional PK data from this study and re-evaluation of data submitted in earlier supplements, the review team revised dosing recommendations for both adults and children. These data confirmed the interaction between LPV/RTV and NVP resulting in lower exposure to LPV when the drugs are given in combination as they were in Study M98-888. LPV/RTV was shown to be effective at the approved study dose. However, because of the reduced concentrations of LPV, it is now recommended that patients receiving concomitant NVP (or efavirenz) receive 533 mg LPV/133 mg RTV twice daily regardless of their previous treatment history or perceived risk of HIV resistance. Children receiving both LPV/RTV and NVP (or efavirenz) should receive a correspondingly higher weight-based (or body surface area-based) dose.

E. Special Populations

This supplement identified no issues in special populations that warrant special labeling. The number of women enrolled in this study was too small to draw any conclusions regarding activity or gender-specific safety problems. Similarly, ethnic minority patients made up a relatively small proportion of those enrolled in Study M98-888. As part of a Phase 4 requirement, the sponsor submitted a meta-analysis comparing the efficacy of LPV/RTV in Black patients and Caucasians across their clinical trial database. While the meta-analysis suggested better response in Caucasian patients, no comparable data is available for other antiretroviral drugs.

There was no additional pediatric data presented in this submission. LPV/RTV has been approved for use in children > 6 months of age and is planned for study in infants < 6 months of age in collaboration with the Pediatric ACTG.

Clinical Review

I. Introduction and Background

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

Kaletra (lopinavir/ritonavir, ABT-378, LPV/RTV) is a co-formulation of two antiretroviral drugs in the class of HIV protease inhibitors (PIs). Lopinavir (LPV) serves as the active antiretroviral compound while ritonavir (RTV) serves, in this instance, as a pharmacologic enhancer by inhibiting the metabolism of LPV via the CYP3A system. Abbott Pharmaceuticals submits this efficacy supplement in support of Traditional Approval for Kaletra in fulfillment of their post-marketing agreement to provide long-term clinical trials (Subpart H). This submission includes 48-week data from a single trial of Kaletra in HIV-infected adults, Study M98-888. The dose of Kaletra evaluated in the study is 400 mg LPV/100 mg RTV given twice daily in combination with nevirapine (NVP) and two nucleoside reverse transcriptase inhibitors (NRTIs) compared to either single or dual investigator-selected protease inhibitor (ISPI) also in combination with NVP and two NRTIs.

B. State of Armamentarium for Indication(s)

Protease inhibitors have become the mainstay of highly active antiretroviral therapy when given in combination with nucleoside reverse transcriptase inhibitors (NRTIs). Combinations of 3 or 4 antiretroviral drugs are now standard therapy in North America and Europe and are gradually being adopted in more resource-poor countries as cost containment strategies are being implemented. The development of resistance to these agents continues and the need for new drugs with improved resistance profiles remains critical. Many of the currently available antiretroviral drugs also have significant adverse effects and drugs with better tolerability and toxicity profiles are also needed. Based on the data previously reviewed, it is anticipated that Kaletra has an acceptable safety profile and may have a resistance profile that allows its use in patients who have failed therapy with some other PIs.

C. Important Milestones in Product Development

The capsule and oral solution co-formulations of Kaletra have both been studied under IND [redacted] e adult Phase III treatment studies submitted under NDA 21-226 (soft gel capsule formulation) and the pediatric Phase II/III study submitted under NDA 21-251 (oral solution formulation) were received in May, 2000 and reviewed simultaneously. An interim report of Study M98-888 was reviewed as part of the original NDA package. Both the capsule and oral solution formulations of Kaletra were granted accelerated approval on the basis of 24-

week data showing declines in HIV-1 RNA levels and improvements in CD4 cell counts over the 24-week study period. Original approval was granted September 15, 2000. 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 the 48-week results were incorporated into the product label. The current submission completes the sponsors requirements for Traditional Approval.

D. Other Relevant Information

Kaletra has been approved in 74 other countries including those belonging to the European Union.

E. Important Issues with Pharmacologically Related Agents

Many of the protease inhibitors (PIs) already approved for use in the treatment of HIV infection exhibit significant drug-drug interactions because of inhibition and/or induction of the hepatic cytochrome P450 enzymes. Ritonavir is the prototype PI for these interactions through inhibition of CYP3A4 and is used in the LPV/RTV co-formulation specifically as a pharmacologic enhancer to slow its metabolism and boost LPV concentrations. Because of the known drug-drug interactions between RTV (and therefore LPV/RTV) and other drugs metabolized via the CYP3A4 isoenzyme, Abbott and other sponsors have conducted studies evaluating the PK profile of LPV/RTV in combination with other antiretroviral drugs (eg. amprenavir, saquinavir, delavirdine) and a variety of other medications. These have been reviewed in detail during the original NDAs and the 48-week sNDA and drug interaction data are prominently displayed in the product label.

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

There are no new clinically relevant findings from chemistry or pharmacology/toxicology submitted with this supplement. These data were reviewed in detail in conjunction with the original NDA. The current submission does not contain new data related to HIV resistance to LPV/RTV but the sponsor provided a submission to IND 51,715 (SN 617) containing a review of resistance data which has been reviewed by the Microbiology Reviewer, Dr. Julian O'Rear. Efficacy data has been evaluated by the Mathematical Statistics Reviewer, Dr. Rafia Bhore. Please refer to the Statistical Review of this supplement for details of her analysis. Also additional pharmacokinetic data has been submitted to IND [redacted] and cross-referenced to this supplement that clarifies the drug-drug interaction between LPV/RTV and NVP.

complete description of the study population demographics and extent of drug exposure can be found in the Integrated Review of Safety. Table 1 summarizes patient participation by country.

Table 1: Subjects Enrolled in Study M98-888 by Country

Country	Number Screened	Number Randomized	Number Enrolled
Australia	3	2	2
Brazil	36	28	28
Canada	34	28	27
Denmark	6	5	5
England	5	4	4
France	6	6	6
Germany	10	7	7
Poland	8	8	8
Spain	46	32	32
South Africa	14	12	12
United States	253	162	150
Puerto Rico	10	7	7
Total	431	301	288

Table 2 summarizes the disposition of all patients screened for Study M98-888 at all sites.

Table 2: Disposition of Subjects in M98-888

Disposition	Number of Subjects
Total number screened	431
Did not meet entry criteria	114
Laboratory value exclusion	14
HIV RNA < 400 copies/mL at screening	61
Not randomized, other reasons*	32
Lost to follow-up prior to randomization	5
Withdrew consent prior to randomization	16
Randomized but never dosed	13
Randomized and received drug	288
Subjects on study ≥ Week 48	192

*Other reasons include: anticipated noncompliance (7), acute illness (1) and unstated reasons (26).

C. Postmarketing Experience

During the course of the review, a brief case report describing 2 Japanese patients with serious bradycardic arrythmias presumed to be associated with LPV/RTV use was published (Clin Infect Dis 2002;35:488-90). Based on this publication, the sponsor was asked to provide an analysis of EKG abnormalities in all Phase 2 and Phase 3 clinical trials and cardiac clinical events reported in clinical trials and to their postmarketing surveillance system. An evaluation of bradycardic arrhythmias reported to the FDA's Adverse Event Reporting System (AERS) was also conducted. Review of these analyses are included in the Integrated Review of Safety and a copy of the CID case report is included as Appendix 1.

V. Clinical Review Methods

A. How the Review was Conducted

Study M98-888 was reviewed for both safety and efficacy. The sponsor's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. Dr. Rafia Bhore performed the statistical analysis confirming the primary endpoint and some subgroup analyses. The MO reviewed study design, patient demographics, adverse events and laboratory safety monitoring data and some secondary efficacy results using the JMP Statistical Discovery software. In this review, tables that were derived from the sponsor's submission are cited as to source in the table footnotes, while those that are derived from reviewer-generated results are not referenced.

B. Overview of Materials Consulted in Review

The 64 volumes of material documenting the results of Study M98-888 as presented in Abbott's Final Study Report and their conclusions regarding the study were used as the primary data source in this review.

Clinical Information Amendment (SN 620) submitted to IND 51,715 provides an analysis of the efficacy and safety of LPV/RTV in Caucasian and Black patients enrolled in 7 clinical trials conducted by Abbott. This analysis fulfills a Phase 4 commitment requested at the time of approval of NDA 21-226, S-003. The report was reviewed and pertinent information is included in Section IX - Use in Special Populations later in this document.

The sponsor also provided a summary of pre-clinical data related to potential cardiac toxicity in a Pha[illegible]acology/Toxicology Information Amendment (SN 631) submitted to IND [illegible] This submission includes an integrated pharmacology report of the *in vitro* effects of LPV/RTV in HERG tail current and Purkinje fiber

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

A significant PK interaction between LPV/RTV and NVP was identified in the pediatric clinical trial. Concomitant administration of these drugs in children resulted in a decrease in LPV exposure of about 30%. Similar interactions were found between LPV/RTV and efavirenz in an adult clinical trials. Study M98-888 collected PK data from treatment experienced adults receiving LPV/RTV and NVP concomitantly. These data have been reviewed by Dr. Derek Zhang, the Clinical Pharmacology and Biopharmaceutics reviewer, and confirm that exposure to LPV/RTV is significantly decreased when the drug is given in combination with NVP. Both AUC and C_{max} for LPV are 25-30% lower and C_{min} is about 40% lower than when LPV/RTV is given without concomitant NVP.

B. Pharmacodynamics

This supplement contains data from a clinical trial using only the currently approved dose of 400mg LPV/100 mg RTV; no new pharmacodynamic data is presented with this submission.

IV. Description of Clinical Data and Sources

A. Overall Data

This submission contains data from a single adult study, M98-888. The sponsor has also submitted an analysis of cardiac events including data from post-marketing surveillance, compassionate access protocols, and reviews of the literature.

This submission contains 64 volumes of material documenting the study results, Abbott's conclusions regarding Study M98-888 48-Week Report, and proposed label revisions. The paper copy is the official submission. In addition, CDs containing copies of the CRTs and CRFs have been submitted as a reviewer's aid. The CDs contain datasets as SAS transport files of demographic, safety and efficacy data through 48 weeks. Comparisons of data from the reviewer's aid CD and the study report line listings supported the sponsor's assertion that the electronic datasets were a true representation of the data in the paper submission.

B. Tables Listing the Clinical Trials

Only a single clinical trial is submitted for review, Study M98-888. The study was conducted by the sponsor and utilized 76 principal investigators in 11 countries, enrolling from one to 13 study subjects each. Sixty-four percent of patients enrolled were from North America and 22% were from Europe. A more

[redacted] assays. This summary had been requested by regulators at the EMEA and a copy of the same information was submitted in SN 631. Some of this data was reviewed with the original NDA.

During the review period, the sponsor was asked to provide additional data regarding cardiac adverse events from their combined safety databases and additional analysis of EKG data collected during Study M98-888 because of the case reports of bradyarrhythmias. This information is contained in an amendment, dated 10/10/02. Review of this material is incorporated into the Integrated Review of Safety.

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

No DSI audit was requested during the review of this NDA supplement.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states that the study was conducted according to accepted ethical standards based on the precepts established by the Declaration of Helsinki. Copies of the study protocol and all protocol amendments and a sample Informed Consent Form are included in the submission as is a list of the IRBs responsible for local oversight of the protocol at each study site. The sponsor notes that it was the responsibility of the individual investigators to ensure that subjects were given adequate information to assess the potential risks and benefits of study participation. There is no clear documentation of how this was evaluated for each site.

E. Evaluation of Financial Disclosure

Abbott Laboratories submitted with this application the required certification and disclosure of financial interests and arrangements with clinical investigators participating in M98-888 (Form FDA 3454 and Form FDA 3455). Three investigators disclosed significant financial arrangements and interests with the sponsor in the form of payments from Abbott having value in excess of $25,000, other than payment for conducting Study M98-888. Two of these investigators enrolled no patients in the study and the third was a sub-investigator at a site that enrolled 4 subjects. Because of the small number of subjects enrolled by these investigators, their participation is not considered to bias the outcome of the study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The results of Study M98-888 confirm the efficacy of LPV/RTV as a component of antiretroviral therapy in a population of HIV-infected adults who were failing a single PI-based regimen. In this study, a greater proportion of patients randomized to receive LPV/RTV in combination with NVP and NRTIs were still responding to therapy after 48 weeks compared to patients randomized to receive ISPI plus NVP and NRTIs. Through Week 48, 57% of LPV/RTV patients achieved and maintained a virologic response of HIV RNA < 400 copies/ml while only 33% of ISPI patients maintained this level of viral suppression. Among patients who had both baseline and Week 48 values available for analysis, both treatment groups exhibited significant increases in mean CD4 cell counts and decreases in mean log change in HIV RNA over the 48 week study period. The sponsor's proposed revisions to the product label were consistent with the data presented.

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

In general, HIV viral load as measured by HIV RNA PCR assays with a lower limit of quantitation of 400 copies/ml was used as the primary measure of the efficacy endpoint. The time to loss of virologic response as defined by the DAVDP antiretroviral drug efficacy algorithm was calculated for the two treatment groups through Week 48 of the study. The proportion of patients still responding at 48 weeks was confirmed by Dr. Rafia Bhore, the Statistical Reviewer. This analysis conforms to one suggested in our recent Guidance for Industry: Antiretroviral Drugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval (10/02). Additionally, measurements of CD4 cells were performed and the mean change from Baseline values was calculated for the two treatment groups at Week 48.

C. Detailed Review of Trials by Indication

1. Summary of study design – Study M98-888

Study M98-888 was a Phase III, randomized, open-label, multi-center, multi-national study comparing LPV/RTV in combination with NVP and 2 NRTIs to a regimen of an investigator-selected protease inhibitor (ISPI) in combination with NVP and 2 NRTIs in antiretroviral treatment experienced patients > 12 years of age. This study report provides data from all 288 patients who were enrolled in the study and received at least one dose of study drugs. Patients randomized to the LPV/RTV arm received the currently approved dose of 400 mg LPV/100 mg RTV orally BID, to be taken with food. Those randomized to the ISPI arm could receive either single or dual PI therapy as described in Table 3. To minimize bias, investigators were asked to choose and document a patient's planned ISPI regimen prior to randomization.

Table 3: Allowed ISPI Regimens in M98-888

Regimen	Study Recommended Dose
Single Protease Inhibitor	
Indinavir	1000 mg Q8H
Saquinavir	1200 mg TID
Ritonavir	600 mg BID
Nelfinavir	750 mg TID
Dual Protease Inhibitor	
Ritonavir/Saquinavir	400 mg RTV/400 mg SQV BID
Ritonavir/Indinavir	400 mg RTV/400 mg IDV BID
Nelfinavir/Saquinavir	1250 mg NFV/1200 mg SQV BID or 750 mg NFV/800 mg SQV TID

Source: M98-888 Final Report, Vol. 1, page 106.

The recommended allowable NRTI regimens included the following: stavudine (d4T) + lamivudine (3TC), zidovudine (AZT) + 3TC, didanosine (ddI) + AZT, ddI + d4T, abacavir (ABC) + d4T, ABC + AZT, ABC + 3TC, ABC + ddI, and zalcitabine (ddC) + AZT. Hydroxyurea at a dose of 500 mg BID could be added to any of the ISPI regimens at the investigator's discretion.

Measurements of vital signs, physical exam, routine clinical laboratory studies, EKGs, and determinations of antiviral and immunologic activity were performed at monthly intervals through Week 24, then every 8 weeks through Week 48, and every 12 weeks after Week 48. Blood samples for resistance testing were archived at each study visit. Clinical adverse events (AEs) were documented at each visit. Guidelines for management of clinical and laboratory toxicity (including discontinuation from study) were provided in the protocol with specific recommendations for the management of hyperglycemia, hypertriglyceridemia, hypercholesterolemia, pancreatitis or amylase elevations, and SGOT or SGPT elevations. Similarly, recommendations were included in the protocol for the management of rash associated with NVP use and ABC hypersensitivity reaction.

Criteria established to define inadequate virologic response were as listed below:

- HIV RNA level did not decrease by at least 1 log by Week 8
- HIV RNA level increased by at least 0.5 log above the nadir at 2 consecutive visits (if nadir > 400 copies/ml)

- HIV RNA level never decreased below 400 copies/ml by Week 24
- HIV RNA level was < 400 copies/ml for 2 consecutive visits prior to Week 24 but then rose above 400 for 2 consecutive visits

Patients who met a virologic endpoint were allowed to continue on study drugs but investigators were encouraged to consider changing antiretroviral therapy. Patients permanently altering dose or regimen were discontinued from study.

2. Study Population

A total of 288 patients were enrolled into Study M98-888; 148 assigned to the LPV/RTV arm and 140 assigned to the ISPI arm.

Major inclusion criteria included:

- Age > 12 years
- Patient had no evidence of acute illness
- Karnofsky score of > 70
- Patient had HIV RNA level > 1000 copies/ml and < 500,000 copies/ml (< 100,000 in the original protocol)
- Patient was currently being treated with a single PI and 2 NRTIs that had not been changed in at least 12 weeks
- At least one new NRTI was available to the patient from among the recommended study NRTIs
- Negative pregnancy test for female participants
- Patient agreed not to take any of the medications contraindicated with PIs and listed in the protocol or in the package inserts for ISPI drugs

Candidates were excluded from the study for any of the following reasons:

- Patient had hemoglobin < 8.0 g/dl, neutrophil count < 750 cells/µl, platelet count < 20,000/µl, SGOT or SGPT > 3 times the upper limit of normal (ULN), or creatinine > 1.5 times ULN
- Patient had received an investigational drug within 30 days prior to screening (except amprenavir)
- Patient had received more than one PI concurrently
- Patient had received treatment with more than one PI for more than 6 weeks prior to their current regimen
- Patient had received prior NNRTI therapy for more than 7 days
- Demonstrated intolerance to NVP
- Patient was receiving systemic chemotherapy
- Patient was felt by the investigator to be unlikely to comply with study procedures

3. Sponsor's Analysis Plan

The sponsor performed an interim efficacy analysis at the time of the original NDA submission, at a time when 118 patients had reached Week 24 of study. At that time, the primary efficacy outcome was the proportion of patients who reached an HIV RNA level < 400 copies/ml at Week 24. Patients in the LPV/RTV arm had a higher response rate with 43/59 (73%) reaching < 400 copies/ml compared to 31/59 (53%) of patients in the ISPI arm ($p = 0.02$).

The efficacy analyses for this submission were performed on all 288 participants who took at least one dose of study drug. The analyses were performed after the last eligible patient reached Week 48. For their analyses, the sponsor considered the Week 48 visit to be the visit occurring in the window between Days 309 and 378, closest to Day 336.

The primary efficacy parameter for this analysis was the time to loss of virologic response through Week 48. The sponsor defined time to loss of virologic response as the first occurrence of either 2 consecutive visits with HIV RNA level > 400 copies/ml, the addition of a new antiretroviral agent (other than protocol-allowed switches in NRTIs), or treatment related premature discontinuation from study. These criteria applied to patients who achieved an HIV RNA < 400 copies/ml by Week 24. Patients who failed to reach an HIV RNA < 400 were considered to have loss of virologic response at Day 1.

The sponsor provided several secondary efficacy analyses. These included the following:

- Proportion of patients with HIV RNA level < 400 copies/ml at Week 48
- Proportion of patients not experiencing a virologic endpoint at Week 24
- Proportion of patients with HIV RNA < 400 at each time point
- Time to HIV RNA nadir
- Time to first HIV RNA < 400 copies/ml
- Change from baseline to each visit in HIV RNA level, CD4 cell count, and CD8 cell count
- AUCMB for HIV RNA level, CD4 and CD8 cell counts through Week 16, Week 24 and Week 48

Safety analyses were conducted including all patients who received at least 1 dose of assigned study drug and had any post-baseline data available. Both laboratory abnormalities and clinical AEs were analyzed.

4. Study Population Baseline Characteristics

Subjects enrolled in Study M98-888 had the following baseline demographic and disease characteristics (see Tables 4 and 5). Patients in the study were balanced across the treatment arms in terms of age, sex, ethnicity, baseline HIV RNA level, and baseline CD4 and CD8 cell counts.

Table 4: Demographic Characteristics of Study Subjects

Characteristic	LPV/RTV Patients (N = 148)	ISPI Patients (N = 140)	All Enrolled Patients (N = 288)
Gender			
Male	125 (84%)	124 (89%)	249 (86%)
Female	23 (16%)	16 (11%)	39 (14%)
Age			
Mean (years)	40.4	40.4	40.4
Range	18-73	25-71	18-73
Race/Ethnicity			
Black	30 (20%)	22 (16%)	52 (18%)
Caucasian	115 (78%)	115 (82%)	230 (80%)
Hispanic*	16 (11%)	21 (15%)	37 (13%)
Asian/Pacific Islander	1 (<1%)	2 (1%)	3 (1%)
Native American/Alaskan	1 (<1%)	1 (<1%)	2 (<1%)
Mixed/Other	1 (<1%)	0	1 (<1%)
Height (mean, in cm)	173.5	173.4	173.5
Weight (mean, in kg)	74.7	75.2	74.9

Source: Study M98-888-Final Report, Vol. 1, page 162.
*"Hispanic" was sometimes listed in addition to either "Black" or "Caucasian"

Table 5: Baseline Disease Characteristics (mean)

	LPV/RTV (N = 148)	ISPIs (N = 140)
HIV RNA Level (log_{10} copies/ml)*	4.11	4.15
Subjects with Baseline HIV RNA Level $\geq 10^5$ (%)	22 (14.9%)	22 (15.7%)
CD4 Cell Count (cells/μl)**	315	332
CD8 Cell Count (cells/μl)	939	1017

*For Baseline HIV RNA, N = 144 for LPV/RTV and N = 136 for ISPI.
**For Baseline CD4 cell count, N = 147 for LPV/RTV and N = 140 for ISPI

Minor differences were noted between this reviewer's calculations of baseline mean values for HIV RNA levels and CD4 cell counts and the sponsor's. These were not significant in the overall analysis and were likely due to slightly different methods of calculating the Baseline value. The sponsor routinely averaged the last 2 values prior to starting drug (eg., Baseline and Screen, Baseline and Randomization, or Screen and Randomization) to obtain their Baseline value. This reviewer used the last value prior to starting drug (eg., Baseline or Screen or Randomization if Baseline was missing).

The proportions of patients receiving other antiretroviral drugs prior to enrollment in this study are summarized in Table 6. Prior to enrollment on the study, the most commonly received PIs were indinavir and nelfinavir and the most common NRTIs were AZT and 3TC. These therapeutic choices are fairly typical of clinical practice at the time the study was enrolling.

Table 6: Prior Antiretroviral Drug Use*

	LPV/RTV (N = 148)	ISPIs (N = 140)
Protease Inhibitors		
Indinavir	66	56
Nelfinavir	62	62
Ritonavir	13	21
Saquinavir (Invirase)	12	13
Saquinavir (Fortovase)	12	9
Amprenavir	3	2
Nucleoside Reverse Transcriptase Inhibitors		
Zidovudine	100	105
Lamivudine	99	98
Stavudine	60	60
Didanosine	50	55
Combivir	35	36
Zalcitabine	26	21
Abacavir	1	2
Non- Nucleoside Reverse Transcriptase Inhibitors		
Efavirenz	1	0
Nevirapine	0	1
Other Antiretroviral Therapy		
Hydroxyurea	7	3
Other	1	2

*Patients may have received more than 1 drug per medication class.
Source: Study M98-888-Final Report, Vol. 1, page 164.

Investigators selected a dual PI regimen in a majority of patients assigned to the ISPI arm with 70.7% receiving dual PIs and 29.3% receiving a single PI. As shown in Table 7, 29/41 patients receiving a single PI received nelfinavir and 62/99 patients receiving dual PI therapy received the combination of ritonavir/saquinavir. These PI selections reflect the recommendation to provide a new PI regimen in patients who had most often received indinavir alone or nelfinavir alone before study entry.

Table 7: Summary of PI Regimens in the ISPI Treatment Group

ISPI Regimen	Number receiving (N = 140)
Single PI	41 (29.3)
Indinavir	8 (5.7%)
Nelfinavir	29 (20.7%)
Ritonavir	3 (2.1%)
Saquinavir	1 (0.7%)
Dual PI	99 (70.7%)
Ritonavir/Indinavir	29 (20.7%)
Ritonavir/Saquinavir	62 (44.3%)
Saquinavir/Amprenavir*	1 (0.7%)
Saquinavir/Nelfinavir	7 (5.0%)

*SQV/APV not a protocol specified ISPI regimen.
Source: Study M98-888-Final Report, Vol. 1, page 166.

5. Efficacy Analysis

Overall, 192 of 288 patients remained on Study M98-888 to Week 48 or beyond, 112 in the LPV/RTV arm and 80 in the ISPI arm. The difference in premature discontinuations was statistically significantly different between the two treatment arms with 24.3% of patients in the LPV/RTV arm leaving study prematurely and 42.9% of those in the ISPI arm leaving prematurely. Greater proportions of patients in the ISPI arm withdrew prematurely because of adverse events, HIV-related events, or virologic failure than did those in the LPV/RTV arm. The protocol did not require that patients withdraw from the study after meeting a virologic efficacy endpoint but all patients who withdrew prematurely due to virologic failure had met a virologic endpoint. Treatment outcomes will be discussed more fully later in this section of the review.

Protocol deviations did occur during the study. The sponsor considered most of these minor. Most of the protocol deviations were related to failure

to meet entry criteria although there were a small number of protocol therapy errors. The protocol deviations are summarized in Table 8. Because there was an imbalance between arms in the number of patients who had received a second PI for greater than 6 weeks prior to study and in the number of patients who failed to receive NVP, the sponsor conducted efficacy analyses both including and excluding these patients. Their sensitivity analyses suggested that these imbalances had no significant impact on the efficacy results.

Table 8: M98-888 Protocol Deviations

Protocol Deviation	LPV/RTV Arm (N=148)	ISPI Arm (N=140)
Entry Criteria Deviations		
HIV RNA level outside entry criteria	5	2
Clinical laboratory abnormality	5	4
Changed antiretroviral therapy within 12 weeks prior to study	29	40
Received more extensive than allowed PI therapy prior to study	8	12
Received ≥ 3 NRTIs concurrently prior to therapy	5	1
Received more extensive than allowed NNRTI therapy prior to study	2	0
Received more extensive than allowed PI and NRTI therapy prior to study	0	1
On Protocol Errors		
Did not receive NVP correctly as defined in protocol Received no NVP	1 0	8 5
Received non-protocol ISPI regimen (saquinavir/amprenavir)	0	1
Received protocol excluded concurrent drug	1	1

The primary efficacy outcome for this study was the time to loss of virologic response as defined by the DAVDP's antiretroviral drug efficacy algorithm. For the details of this algorithm, please refer to the Statistical Review conducted by Dr. Rafia Bhore. In brief, this endpoint was defined as the first of two consecutive HIV RNA measurements above 400 copies/ml after a patient achieved a confirmed response (HIV RNA below 400 copies/ml on two consecutive measurements). Patients who required a switch of therapy or who discontinued therapy because of adverse events were considered response failures at the time of those events and patients who never achieved a confirmed response were considered response failures on Day 1.

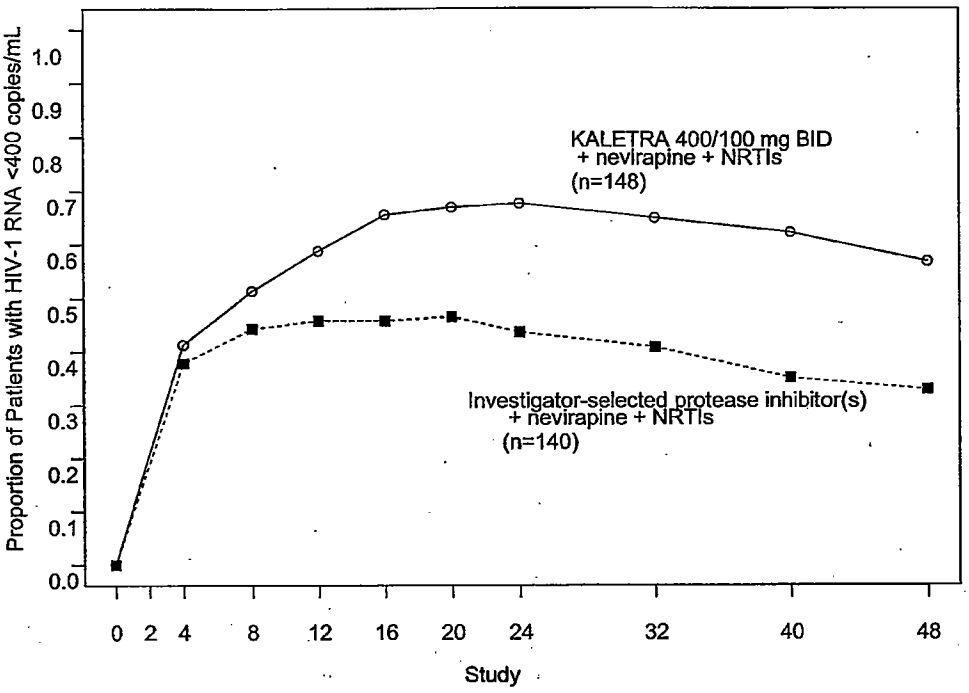
There was a statistically significant difference in the time to loss of virologic response favoring the LPV/RTV arm. After 48 weeks of therapy, 57% of those receiving LPV/RTV maintained their virologic response compared to 33% of those receiving ISPI regimens. These data are presented in Table 9 and in the Kaplan-Meier estimates of the proportion of patients still responding to therapy through 48 weeks as shown in Figure 1. Dr. Bhore's analysis confirmed the sponsor's analysis of the primary endpoint. It should be noted that the category of "death" as a treatment outcome includes only those patients for whom death was the event leading to premature discontinuation. Two additional patients died during study after reaching another study endpoint.

Table 9: Outcomes of Treatment in Study M98-888 through 48 Weeks

Outcome	Kaletra Arm (N=148)	ISPI Arm (N=140)
HIV RNA < 400 copies/mL	84 (57%)	46 (33%)
HIV RNA > 400 copies/mL	35 (24%)	58 (41%)
Rebound	16 (11%)	26 (19%)
Never suppressed	19 (13%)	32 (23%)
Death	1 (1%)	3 (2%)
Discontinued due to adverse events	7 (5%)	15 (11%)
Discontinued due to other reasons*	21 (14%)	18 (13%)

*This category includes non-adherence, lost to follow-up, patient required prohibited medication, personal reasons, admission criteria violations and other similar reasons.

Figure 1: Kaplan-Meier Estimates of Proportion of Patients Still Responding to Therapy through Week 48



The sponsor analyzed the secondary endpoint, the proportion of patients with undetectable viral load, using different populations and analyses. In general, the Division prefers the more conservative intent-to-treat (ITT) analyses in which missing data is considered to be above 400 copies/ml if not immediately flanked by values below 400 copies/ml (NC=F) or if missing for any reason (M=F). The on-treatment analysis has the disadvantage of evaluating only those patients who are able to continue on study therapy for the duration of the study period but does not account for patients who have failed therapy prior to that time. Similarly, the intent-to-treat analysis that replaces a missing data point by carrying forward the last available value does not fully account for patients who may have left the study prior to Week 48 (LOCF).

As shown in Table 10, a significantly greater proportion of patients in the LPV/RTV arm achieved an HIV RNA level < 400 copies/ml at Week 48 compared to those receiving ISPI when using the ITT (M=F) or ITT (NC=F) populations. In these analyses, 54% of patients receiving

LPV/RTV had HIV RNA < 400 copies/ml after 48 weeks of dosing compared to 39% in the ISPI arm. Statistical significance was lost when the analyses used the on-treatment group or when the ITT (LOCF) analysis was used. In the on-treatment group, the number of patients included was much smaller and a disproportionate number left the ISPI arm. Although the numbers are too small to make definite conclusions, it appeared that patients in the ISPI arm who received dual PI therapy achieved better responses than those who received only single PI therapy. In the sponsor's subgroup analysis, LPV/RTV provided significantly better response rates than the single PI regimens over 48 weeks compared to the dual PI regimens.

Table 10: Proportion of Patients with HIV RNA Levels < 400 copies/ml at Week 48

Analysis Group	LPV/RTV (N=148)	ISPI		
		Single PI (N=41)	Dual PI (N=99)	All ISPI (N=140)
ITT (M=F)	80/148 (54%)	13/41 (32%)*	41/99 (41%)	54/140 (39%)*
ITT (NC=F)	80/148 (54%)	13/41 (32%)*	41/99 (41%)	54/140 (39%)*
ITT (LOCF)	94/148 (64%)	18/41 (44%)*	56/99 (57%)	74/140 (53%)
On Treatment	79/101 (78%)	12/21 (57%)	40/50 (80%)	52/71 (73%)

Source: Study M98-888-Final Report, Vol. 1, pages 171 and 174.
*P-values at the 0.05 level or less.

In both the sponsor's review and my review, patients in both treatment arms had significant mean log decreases in HIV RNA over the study period. There was no significant difference in the mean log change in viral load between the two treatment arms as summarized in Table 11 below. Similarly, both treatment groups exhibited increases in mean CD4 cell counts during the study period as shown in Table 12. Again there was no significant difference in the mean CD4 increase between the treatment groups. Through 48 weeks of study, very small increases were seen in mean CD8 cell counts in both treatment groups. As previously noted, this reviewer's calculations for the mean changes from Baseline were slightly different from the sponsor's. These differences can be attributed to minor differences in determining the Baseline value for some patients.

Table 11: Mean Log Change in Viral Load at Week 48*

	LPV/RTV Arm	ISPI Arm
Mean Log HIV RNA at Baseline	3.99	3.98
Mean Log HIV RNA at Week 48	2.89	3.01
Mean Log Change in HIV PCR from Baseline	-1.09	-0.96

*Calculations are based on number of subjects with both baseline and Week 48 values; N = 95 for LPV/RTV arm and N = 56 for ISPI arm. For some patients, Screening or Randomization visit values were used in place of missing Baseline values.

Table 12: Mean Changes in Absolute CD4 Cell Counts through Week 48 (cells/μl)*

CD4 Cell Count	LPV/RTV	ISPIs
Baseline	317	359
Week 48	417	455
Change from Baseline to Week 48	100	96

*Calculations are based on number of subjects with both baseline and Week 48 values; N = 93 for LPV/RTV and N = 55 for ISPI. For some patients, Screening or Randomization visit values were used in place of missing Baseline values.

D. Efficacy Conclusions

The results of Study M98-888 confirm that LPV/RTV is an effective component of combination antiretroviral therapy in adults who have previously been treated with another PI-containing regimen. In this study, patients were randomized to receive either LPV/RTV or an alternate single or dual PI selected according to the investigator's best judgement. Both treatment groups also received NVP, an antiretroviral drug from a class new to the patient, and two NRTIs, at least one of which was new to the patient. At the time this study was begun, this was considered an appropriate approach to choosing an optimal therapeutic regimen, although currently HIV genotyping is used to aid in selection of new antiretroviral regimens.

In this population, a greater proportion of patients receiving LPV/RTV achieved and maintained viral suppression of HIV through 48 weeks than did those who received ISPI regimens, 57% compared to 33%. A greater proportion of patients in the LPV/RTV group remained on study through the entire study period with more patients prematurely discontinuing in the ISPI arm due to adverse events, HIV-related events, and virologic failure. Both treatment groups achieved similar, significant decreases in mean log change from Baseline in HIV RNA and increases in mean CD4 cell counts over the 48 week study period.

In retrospect, it might have been more appropriate to compare LPV/RTV to only dual ISPI regimens since the dual regimens also provide a PI pharmacologically boosted with ritonavir. In a subgroup analysis conducted by the sponsor, the single ISPI regimens were less efficacious than the LPV/RTV regimen. Numerically, the dual ISPI group had efficacy greater than the single ISPI group and less than the LPV/RTV group but the study was not designed or powered adequately to draw conclusions about differences between the dual ISPI regimen and LPV/RTV.

The sponsor chose to use the standard, approved dose of 400 mg LPV/100 mg RTV given twice daily in this study. Data from the pediatric study suggests that a drug interaction between LPV/RTV and NVP might result in lower LPV concentrations when the drugs are given concomitantly. Similar reductions in LPV concentrations were seen in adults when LPV/RTV was given in combination with efavirenz. However, an adult PK study of concomitant LPV/RTV and NVP failed to show the same degree of interaction as seen in the pediatric study. In an adult study (M98-957), it appeared that treatment responses were better when a higher dose of 533 mg LPV/133 mg RTV was provided for patients with significant previous PI therapy. PK data from Study M98-888 confirms that LPV exposure is decreased when the drug is given in combination with NVP. Therefore, it is certainly possible that treatment response in this population might have been even better if a higher dose of LPV/RTV was used. However, the studied dose of LPV/RTV was still significantly more effective than the comparator regimens.

The submitted data for Study M98-888, in combination with data previously presented from other clinical trials, provides the final data needed to grant Kaletra (LPV/RTV) Traditional Approval for the indication of treatment of HIV infection in combination with other antiretroviral drugs. LPV/RTV has been shown to be effective in suppressing HIV replication in patients who are both treatment naïve (previously reviewed) and treatment experienced (current review) over study periods of at least 48 weeks.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

LPV/RTV was found to be safe and relatively well-tolerated in this population of PI-experienced, HIV-infected adults over a period of 48 weeks in comparison to ISPI regimens. The toxicity profile of LPV/RTV was similar to that described in other studies reviewed for earlier NDA submissions. Not surprisingly the proportions of patients developing adverse events and presumed toxicity increased from the time of the interim report to the final study report.

The most common AEs reported were gastrointestinal complaints and hyperlipidemia. Among AEs that were moderate or severe in intensity and considered drug related, nausea and vomiting were reported more commonly among patients receiving ISPI regimens than among those receiving LPV/RTV. If events of all intensity were considered, gastrointestinal events (anorexia, diarrhea, nausea, and vomiting) were reported in similar proportions of patients in both treatment arms and occurred in up to 45%. Patients receiving ISPI regimens were more likely to require premature discontinuation from study because of AEs. A small number of deaths were reported during the study with no differences between treatment arms.

Isolated Grade 3 or 4 laboratory abnormalities were also common during the study but were balanced across the treatment arms. Hyperlipemia and hypercholesterolemia were the most frequently identified laboratory abnormalities and occurred in 20 to 25% of patients in the study. As noted above, the profile of laboratory abnormalities was not significantly different than that reported during previous LPV/RTV studies in treatment experienced patients.

B. Description of Patient Exposure

Study M98-888 provides safety data for 288 patients who were randomized to receive either LPV/RTV or ISPI in combination with NVP and NRTIs. The duration of therapy ranged from 2 days to 378 days. A majority of patients in both treatment arms received study drugs for over 48 weeks, although the median length of therapy was longer in the LPV/RTV group than in the ISPI group. These data are summarized in Table 13. All patients randomized to the LPV/RTV treatment arm received the same dose of study drug, 400 mg LPV/133 mg RTV taken twice daily. Doses of drugs administered in the ISPI arm were the standard, approved doses.

Table 13: Study Drug Exposure Through Week 48

Study Drug Exposure (days)	LPV/RTV Arm (N = 148)	ISPI Arm (N = 140)
1 – 28	8 (5.4%)	10 (7.1%)
> 28 – 56	2 (1.4%)	6 (4.3%)
> 56 – 112	7 (4.7%)	9 (6.4%)
> 112 – 168	4 (2.7%)	11 (7.9%)
> 168 – 252	8 (5.4%)	11 (7.9%)
> 252 – 336	20 (13.5%)	26 (18.6%)
> 336	99 (66.9%)	67 (47.9%)
Median (days)	372	335

Source: Study M98-888-Final Report, Vol. 1, page 188.

C. Methods and Specific Findings of Safety Review

All 288 patients who received at least one dose of study drug in Study M98-888 were included in the sponsor's safety analysis. Adverse events (AEs) were recorded for every patient at each study visit. Investigators at each site graded the intensity of the event (mild, moderate, or severe) and the perceived relationship to study drug (not related, probably not related, possibly related, or probably related). Serious adverse events (SAEs) were those events resulting in: death, life-threatening situation, hospitalization, persistent or significant disability, congenital anomaly, or other important medical event. AEs and SAEs were coded and compiled by the sponsor according to COSTART terms describing medical conditions. Laboratory studies including routine hematology and clinical chemistry studies were monitored at every study visit. Additional monitoring, such as electrocardiograms (EKGs) were performed at designated visits during the study. The safety analysis provided by the sponsor included descriptive analyses of the compiled AEs and SAEs, evaluation of changes over time in laboratory test values, and the occurrence of "extreme" (very high or very low) laboratory values defined by the protocol. As previously mentioned, additional review of cardiac arrhythmia clinical events was requested during the review. This information has been incorporated into the safety review. The sponsor's analysis and conclusions were confirmed by review of the line listings and electronic datasets provided in this submission.

Patients who still satisfied the on-study criteria were allowed to continue on study drug beyond 48 weeks and were followed for safety during this time. Safety data collected beyond 48 weeks was not reviewed in detail but was generally similar to that collected during the first 48 weeks.

Adverse Events

AEs were commonly reported during the study with > 95% of patients in both treatment arms describing at least one AE. Most of these events were considered mild and did not interfere with patients' participation in the study. Many of the reported AEs represent conditions that are common in HIV disease and with the use of antiretroviral drugs. A total of 2914 AEs were reported during the study period, however, in many cases multiple COSTART terms were listed describing the same episode. For example, an illness characterized by nausea, vomiting and diarrhea might be coded as the three separate AEs. Table 14 below summarizes the most frequent AEs reported during the study.

Table 14: Adverse Events Reported by > 10% of Patients in Either Treatment Group Through Week 48, Regardless of Severity or Causality

Body System/Adverse Event	LPV/RTV Arm (N = 148)	ISPI Arm (N = 140)
Body as a Whole		
Abdominal pain	19 (12.8%)	20 (14.3%)
Accidental injury	16 (10.8%)	11 (7.9%)
Asthenia	30 (20.3%)	31 (22.1%)
Back pain	17 (11.5%)	6 (4.3%)
Fever	16 (10.8%)	19 (13.6%)
Flu syndrome	15 (10.1%)	12 (8.6%)
Headache	22 (14.9%)	27 (19.3%)
Infection	19 (12.8%)	17 (12.1%)
Pain	23 (15.5%)	27 (19.3%)
Digestive		
Anorexia	18 (12.2%)	18 (12.9%)
Diarrhea	67 (45.3%)	62 (44.3%)
Nausea	45 (30.4%)	62 (44.3%)
Vomiting	38 (25.7%)	44 (31.4%)
Metabolic/Nutritional		
Hypercholesterolemia	16 (10.8%)	13 (9.3%)
Hyperlipemia	29 (19.6%)	16 (11.4%)
Nervous		
Depression	16 (10.8%)	16 (11.4%)
Insomnia	17 (11.5%)	13 (9.3%)
Paresthesia	14 (9.5%)	16 (11.4%)
Respiratory		
Cough Increased	19 (12.8%)	21 (15.0%)
Pharyngitis	27 (18.2%)	21 (15.0%)
Rhinitis	27 (18.2%)	23 (16.4%)
Skin/Appendages		
Rash	39 (26.4%)	26 (18.6%)

Source: Study M98-888-Final Report, Vol. 1, page 191.

While most AEs were considered tolerable by patients and investigators, 240 of the 288 patients (122 receiving LPV/RTV and 118 receiving ISPI) reported at least one AE described as moderate or severe in intensity. Of these, 137 patients experienced 353 moderate to severe AEs that were judged by the investigator to be possibly or probably related to study drug. The most common AEs of moderate to severe intensity that were thought to be drug related were hyperlipemia, hypercholesterolemia, nausea, diarrhea, vomiting, and asthenia. These events were balanced across the treatment groups except for nausea and vomiting which was see more frequently in the ISPI group. AEs reported in ≥

2% of patients (in either treatment group) and thought to be drug related are summarized in Table 15 and will be included in the revised product label.

Table 15: Adverse Events of at Least Moderate Severity and Considered Possibly or Probably Drug Related, Reported by ≥ 2% of Patients in Either Treatment Group

Body System/Adverse Event	LPV/RTV Arm (N = 148)	ISPI Arm (N = 140)
Body as a Whole		
Abdominal pain	3 (2.0%)	3 (2.1%)
Asthenia	4 (2.7%)	9 (6.4%)
Chills	3 (2.0%)	0 (0%)
Fever	3 (2.0%)	2 (1.4%)
Headache	3 (2.0%)	4 (2.9%)
Digestive		
Anorexia	1 (0.7%)	4 (2.9%)
Diarrhea	11 (7.4%)	14 (10.0%)
Dysphagia	3 (2.0%)	1 (0.7%)
Flatulence	1 (0.7%)	3 (2.1%)
Nausea	10 (6.8%)	23 (16.4%)*
Vomiting	6 (4.0%)	17 (12.1%)*
Metabolic/Nutritional		
Hypercholesterolemia	12 (8.1%)	11 (7.9%)
Hyperlipemia	24 (16.2%)	16 (11.4%)
SGPT Increased	2 (1.4%)	3 (2.1%)
Nervous		
Depression	1 (0.7%)	3 (2.1%)
Insomnia	0 (0%)	3 (2.1%)
Skin/Appendages		
Rash	3 (2.0%)	2 (1.4%)

Source: Study M98-888-Final Report, Vol. 1, page 194.
*AE frequency statistically significantly different between treatment groups at P > 0.05.

In general, the pattern and frequency of these reported AEs was not different from that reported in previous studies of LPV/RTV in adults. When data collected after the 48 week data was included in the analysis, the same types of AEs were reported in similar, but slightly higher, proportions. Gastrointestinal symptoms were among the most common complaints throughout the study period and beyond 48 weeks. These complaints have been well described in previous clinical trials and in clinical practice settings. Hypercholesterolemia and hyperlipemia were reported as AEs inconsistently but were identified more often as laboratory abnormalities and will be discussed in more detail in the section of this review summarizing laboratory findings.

Specific Clinically Significant Adverse Events

Rashes were reported in a large proportion of patients in this study as compared to other studies of LPV/RTV in adults. Seventy-five patients (41 receiving LPV/RTV and 34 receiving ISPI) reported AEs coded as "rash" or "maculo-papular rash". Many of these events were attributed to the use of NVP and a few were attributed to use of ABC, both drugs known to cause rash. Sixteen of these patients (11 LPV/RTV and 5 ISPI) required interruption or dose adjustment of their study drug regimen because of their rashes and one patient prematurely discontinued study after developing a severe (Grade 3) rash. Pharmacokinetic data have shown that co-administration of LPV/RTV and NVP results in lower LPV concentrations but have not identified any change in NVP levels so it is unclear why rash occurred more frequently in patients receiving LPV/RTV.

Six patients, all receiving ISPI, developed AEs identified as hepatitis. One of these patients had acute hepatitis B infection diagnosed on study Day 129. Three patients were noted to have hepatitis C infection documented at Baseline but had no additional serologic tests in the database at the times of their clinical hepatitis AEs. Two of these events were attributed to known hepatitis C infection. The two remaining patients were noted to have drug-induced hepatitis or hepatic toxicity, attributed in one patient to either NVP or ABC and considered probably related to LPV/RTV in the other. Four of the patients experiencing hepatitis AEs required study drug interruption or dose adjustment and two required premature discontinuation from study.

It was more difficult to determine the frequency of body fat composition changes reported as AEs during the study. Since there was no consensus definition for these syndromes during the study period, the database was searched for any COSTART term that might be applicable ("abdomen enlarged", "breast enlargement", "gynecomastia", "obesity", and "lipodystrophy"). Nineteen patients (10 receiving LPV/RTV and 9 receiving ISPI) reported 24 events that could be identified as body fat composition change AEs. All but 3 of these events were thought to be drug related and 19 were graded as mild in intensity. The sponsor identified an additional 5 patients (2 receiving LPV/RTV and 3 receiving ISPI) who had events identified as buffalo hump, Cushing, and other terms possibly compatible with body fat composition changes.

HIV Related Events

Not surprisingly, HIV-related conditions including some AIDS-defining events occurred in the study population. These events were balanced across the treatment arms with 26 LPV/RTV patients and 25 ISPI patients reporting an HIV-related event. The most commonly reported HIV-related events included oropharyngeal candidiasis, herpes simplex, herpes zoster, hairy leukoplakia, Kaposi's sarcoma, and *Mycobacterium avium* complex.

Deaths

There were a total of 6 deaths occurring during the study, 2 patients receiving LPV/RTV and 4 receiving ISPI. One of the ISPI patients died more than 30 days after the last dose of study medication.

Patient #8038's death was initially reviewed during the original NDA submission. This 45 year old female was randomized to receive LPV/RTV but continued to take concomitant methylergonovine maleate (a contraindicated medication), thioridazine hydrochloride, amitriptiline hydrochloride, carbamazepine, and alprazolam. Approximately 3 months after beginning LPV/RTV she presented to the ER with complaints of abdominal pain, constipation and vomiting. Three days later she was hospitalized when she presented comatose, hypotensive, with peripheral vasoconstriction, icterus and abdominal distention. The family noted that the patient had taken methylergonovine for 10 days prior to her first ER visit. Initial evaluation suggested ergotism with ischemic colitis and hepatic encephalopathy. The patient stabilized somewhat but on the fifth hospital day she developed fever, oliguria and hypotension and was ultimately diagnosed with septic shock and multi-organ system failure. Blood cultures drawn at this time yielded a staphylococcus. She died 9 days after hospitalization. The investigator considered the SAEs of ergotism, ischemic colitis, and hepatic encephalopathy to be possibly or probably related to study drug. The event of septic shock was considered probably not related to study drug since an infectious etiology was identified. Clearly, this patient's death is an indirect consequence of study drug related ergotism and ischemic colitis. This case prompted the original NDA review team to develop a risk communication for the drug interaction between LPV/RTV and non-migraine associated ergot alkaloids.

The other reported death in a patient receiving LPV/RTV was patient #8162, a 37 year old male with a past history of tuberculosis, PCP, peripheral neuropathy and Pseudomonas pneumonia. Approximately 2 months after beginning LPV/RTV he began having respiratory symptoms (wheezing and cough) and fever. Reactivation TB was suspected but bronchoscopy identified no specific etiology. He was hospitalized for persistent fevers. A lymph node biopsy revealed caseating granuloma but no acid fast bacilli. Bone marrow biopsy revealed a lymphocytic depleted Hodgkin's lymphoma. Treatment with ethambutol, pyrazinamide, azithromycin and rifabutin was initiated. Approximately 2 weeks after hospitalization study drug and TB treatment were discontinued and the patient was started on prednisone. The next day his blood pressure, heart rate, and oxygen saturation dropped abruptly and he died. The investigator considered the events of TB and lymphoma to be probably not related to study drug.

Less information is available on the patients who died on study while receiving an ISPI regimen. Patient #8016 died following an episode of uncontrolled seizures secondary to a large occipital stroke. This death occurred greater than 30 days

after the patient's last dose of study medications. Patient #8044 died from rectal bleeding secondary to a squamous cell carcinoma of the rectum. Patient #8098 was found in an alley, dead from a suspected street drug overdose. Patient #8107 was diagnosed with Kaposi's sarcoma on Day 60 and received both chemotherapy and radiation while remaining on study. He was hospitalized on Day 439 of study with fever, acidosis, hypoxemia, thrombocytopenia, and adult respiratory distress syndrome thought to be due to pulmonary KS with secondary PCP or other infection and died 12 days later. None of these deaths was considered related to study medications.

Serious Adverse Events

During the 48 week study period 33 patients (17 receiving LPV/RTV and 16 receiving ISPI) experienced 57 SAEs, not HIV related or resulting in death. Of the 57 reported SAEs, 51 were considered not related or probably not related to LPV/RTV while only six were considered possibly or probably related to study drug. However, 12 of these patients required interruption or dose adjustment of study medication and four required premature discontinuation from study.

Only one patient receiving LPV/RTV had an SAE thought to be drug related. Patient #8211 was hospitalized on Day 235 of study for complaints of shortness of breath, nausea, vomiting, chills, and a rapid heart rate. He was diagnosed with new onset atrial fibrillation and treated medically. Study drug was not interrupted and he recovered from the event with no reported recurrence. The investigator had no alternative explanation for the SAE and considered it possibly related to study drug.

Four patients receiving ISPI developed SAEs thought to be drug related. Patient #8125 developed vomiting, listed as a possible drug reaction with the alcohol in Sporonox. Patient #8139 developed hepatitis thought to be related to drug toxicity. Patient #8178 developed pancreatitis while receiving an ISPI regimen including indinavir, ritonavir, NVP, didanosine and stavudine. Patient #8194 developed abdominal pain with increased abdominal size secondary to lipodystrophy.

Premature Discontinuations Secondary to Adverse Events

A search of the database identified 31 patients who were listed as premature discontinuations from study because of AEs. These included 8 patients receiving LPV/RTV and 23 patients receiving ISPI. In the Final Study Report the sponsor identified as premature discontinuations an additional 3 patients (1 LPV/RTV and 2 ISPI) who died while on study. Table 16 summarizes all 34 patients listed by the sponsor as premature discontinuations. A total of 24 patients (7 LPV/RTV

and 17 ISPI) who discontinued study drug prematurely did so because of AEs that were considered drug related.

Table 16: Adverse Events Leading to Premature Discontinuation

Subject Number	Age/Gender	Descriptive Term(s)	Severity	Relationship to Study Drug
LPV/RTV Treatment Group				
8038	45/Female	Ergotism, sepsis, shock	Severe	Probable
8058	36/Male	Liver function tests abnormal	Moderate	Probable
8162	37/Male	Lymphoma like reaction, TB aggravated, death	Moderate	Probably not
8195	34/Male	Hyperlipemia	Severe	Probable
8208	44/Male	Nausea, vomiting	Moderate	Probable
8216	52/Male	Anorexia, chills, fever, malaise, rash	Moderate to severe	Possible
8253	25/Female	Allergic reaction	Moderate	Probably not
8270	36/Female	Allergic reaction	Moderate	Probable
8271	33/Male	Hyperlipemia	Severe	Probable
Single ISPI Treatment Group				
8079	31/Female	Mycobacterium avium complex	Severe	Not related
8098	34/Male	Death	Severe	Not related
8205	25/Male	Allergic reaction	Moderate	Probable
Dual ISPI Treatment Group				
8016	39/Male	Cerebrovascular accident	Severe	Probably not
8022	46/Male	Headache, nausea, vomiting	Mild to moderate	Probable
8041	25/Male	Allergic reaction	Moderate	Not related
8044	71/Male	Gastrointestinal carcinoma, deep thrombophlebitis	Severe	Not related
8063	31/Male	Hypercholesterolemia	Moderate	Probable
8070	58/Male	Depression	Severe	Not related
8084	60/Male	Amylase increased	Moderate	Possible
8103	32/Male	Anorexia, nausea, asthenia	Moderate to severe	Probable
8108	34/Male	Hepatitis	Moderate to severe	Probable
8114	50/Male	Diarrhea	Moderate	Probably not
8116	36/Male	Nausea, vomiting	Severe	Probable
8125	34/Male	Vomiting	Moderate	Possible
8139	40/Male	Hepatitis	Severe	Probable
8145	31/Female	Abdominal pain, fever, vomiting	Moderate	Probable
8159	46/Male	Nausea	Mild	Possible

8175	51/Male	SGOT and SGPT increased	Mild	Probable
8178	42/Male	Somnolence, asthenia	Moderate	Probably not
8188	54/Male	Nausea	Mild	Probable
8191	31/Male	Liver function tests abnormal	Severe	Possible
8239	46/Male	Nausea, dry mouth, arthralgia, sweating, circumoral paresthesias, anorexia, asthenia, headache	Mild to Moderate	Probable
8267	53/Male	Lung disorder, myalgia, flu syndrome, asthenia, fever	Mild to severe	Probable
8279	54/Male	SGOT and SGPT increased	Severe	Probable

Source: Study M98-888-Final Report, Vol. 1, page 217-18.
Shaded rows indicate patients who died while on study.

The most common AEs leading to premature discontinuation were elevated liver function tests (also coded as increased SGOT and SGPT), allergic reactions, gastrointestinal conditions, hyperlipemia, and hepatitis. The sponsor noted that patients receiving dual ISPI regimens were more likely than those receiving single ISPI regimens to develop AEs leading to premature discontinuation.

In addition to the patients who prematurely discontinued study medications, there were 85 patients who had their study drug interrupted or dose adjusted because of an AE. AEs caused 46 patients in the LPV/RTV group and 39 patients in the ISPI group to interrupt or adjust their study drug. Of these, 15 LPV/RTV patients and 18 ISPI patients interrupted their study drug regimen because of AEs that were considered drug related. All together 55 LPV/RTV patients (37%) and 64 ISPI patients (46%) either interrupted, dose adjusted or prematurely discontinued their study regimen because of AEs (including patients who died on study).

Clinical Laboratory Findings

The sponsor evaluated clinical laboratory safety data for mean changes from Baseline and for number of patients reaching a designated extreme value (very high or very low). All patients with at least one post-Baseline laboratory value were included in their analyses.

During the 48 week study period, small but statistically significant changes from Baseline were identified in hematology variables in both treatment groups. Mean WBC counts, hemoglobin, absolute neutrophils, absolute lymphocytes, absolute basophils, and percent basophils were increased slightly in both treatment groups. Mean percent monocytes were decreased slightly in both treatment groups. Also, mean hematocrit and platelet count were increased in patients in the LPV/RTV group and absolute monocytes were decreased. There were no statistically significant differences between treatment groups at Week 48 for any hematology

variables and none of the changes over time were considered of clinical significance.

Very few patients had individual hematology variables that were considered extreme (Grade 3 or 4 toxicity as defined in the protocol). Three patients (1 LPV/RTV and 2 ISPI) developed neutropenia ($< 0.75 \times 10^9$/l). Two patients (1 in each group) developed thrombocytopenia ($< 50 \times 10^9$/l). Two patients developed low hemoglobin (< 8.0 g/dl). Abnormal hematology values were inconsistently reported as AEs. Only a single AE of leukopenia was considered drug related. As reported earlier in this review, one patient died from a process that was identified as a lymphoma-like reaction complicated by presumed reactivation TB.

During the 48 week study period, small but statistically significant changes from Baseline were identified in clinical chemistry variables in both treatment groups. These included slight increases in mean alkaline phosphatase, BUN, albumin, calcium, and sodium and larger increases in total cholesterol and triglycerides. Additionally, small mean increases were found in SGOT, SGPT, LDH, and amylase in the ISPI group and in potassium in the LPV/RTV group. Small mean decreases in total bilirubin, total protein, and inorganic phosphorus were found in both treatment groups with mean decreases in uric acid also found in the LPV/RTV group. At Week 48 there were small differences between treatment groups in LDH and uric acid. Increases from Baseline in mean total cholesterol and triglycerides in both treatment arms were considered clinically significant. Similar increases in cholesterol and triglycerides have been observed in clinical trials including other PIs in treatment regimens and were noted in the original NDA review for LPV/RTV.

Marked abnormalities in clinical chemistry values were relatively common during the study period. Eight patients (4 receiving LPV/RTV and 4 receiving ISPI) had at least one extremely low chemistry value. The sponsor identified 112 patients (55 receiving LPV/RTV and 57 receiving ISPI) who had at least one extremely high chemistry value. The proportions of patients developing these extreme clinical chemistry values are listed in Table 17. Extreme laboratory values occurring in $\geq 2\%$ of patients in either treatment group will be displayed in the product label. The most frequently identified extreme laboratory abnormalities included Grade 3 or 4 increases in triglycerides, cholesterol, SGPT, SGOT, and amylase. Each of these abnormalities will be discussed in more detail below.

Table 17: Numbers of Subjects with Extreme Laboratory Values through Week 48 (Grade 3 or 4 Toxicity)

	Indicator Criteria	Kaletra Arm (N=142)*	ISPI Arm (N=131)*
Laboratory Variables Very High			
Total Bilirubin	> 2.9 x ULN	1 (0.7%)	4 (3.1%)
SGOT	> 5 x ULN	7 (4.9%)	14 (10.7%)
SGPT	> 5 x ULN	8 (5.6%)	17 (13.0%)
Cholesterol	> 300 mg/dL	29 (20.4%)	27 (20.6%)
Triglycerides	> 750 mg/dL > 1200 mg/dL	36 (25.3%) 19 (13.4%)	28 (21.4%) 12 (9.2%)
Amylase	> 2 x ULN	5 (3.5%)	10 (7.6%)
Glucose	> 250 mg/dL	2 (1.4%)	3 (2.3%)
Laboratory Variables Very Low			
Sodium	< 123 mEq/L	1 (0.7%)	0
Potassium	< 2.5 mEq/L	0	1 (0.8%)
Calcium	< 7.0 mg/dL	1 (0.7%)	2 (1.5%)
Inorganic phosphorus	< 1.5 mg/dL	1 (0.7%)	0
Magnesium	< 1.0 mEq/L	1 (0.7%)	1 (0.8%)

Source: Study M98-888-Final Report, Vol. 1, pages 233 and 234.
ULN = upper limit of normal value
*Proportion of patients with each laboratory abnormality were calculated based on the number of patients who had at least one post-baseline set of values, N = 142 for Kaletra and N = 131 for ISPI.

Elevated serum lipids were by far the most frequently identified laboratory abnormality in Study M98-888. It should be noted, however, that study laboratory testing was performed without regard for fasting. A total of 64 patients (36 receiving LPV/RTV and 28 receiving ISPI) developed at least one triglyceride value > 750 mg/dL (Grade 3 toxicity). This represents 22% of the study population. Thirty-one of these patients (19 receiving LPV/RTv and 12 receiving ISPI) were found to have a triglyceride value > 1200 mg/dL (Grade 4 toxicity). A total of 56 patients (29 receiving LPV/RTV and 27 receiving ISPI) developed at least one cholesterol value > 300 mg/dL. Many of the patients identified with elevated serum lipids during the study period were documented to have abnormal values at Baseline. Overall, 38 patients had both triglycerides and cholesterol increased to Grade 3 toxicity level during the study. Forty-nine patients (28 LPV/RTV and 21 ISPI) had hyperlipemia and/or hypercholesterolemia reported as an AE of moderate or severe intensity and considered drug related. Most of these patients were treated with medication and remained on study. Only 3 patients required premature discontinuation of study drugs because of elevated lipids, 2 in the LPV/RTV group and one in the ISPI group. The proportion of patients with markedly increased serum lipids was greater in this study than in the previously reviewed Study M98-863, the Phase 3 trial conducted in treatment

naïve patients, but is similar to other studies involving more advanced, PI-experienced patients and was not different between the two treatment arms.

Increased liver transaminases, SGOT and SGPT, were also relatively common in patients participating in Study M98-888. A total of 29 patients (10 receiving LPV/RTV and 19 receiving ISPI) developed at least one SGOT or SGPT value > 5 times the upper limit of normal (a value of about 240 U/L). These numbers represent approximately 11% of the patients with laboratory values available for review (7% of the LPV/RTV group and 15% of the ISPI group). Of this total, 25 patients had elevated levels of SGPT and 21 had elevated SGOT. To explore the possible impact of other illnesses on transaminase levels, this reviewer evaluated the number of patients with documented hepatitis B and/or hepatitis C and elevated SGPT during the study. Of the 25 patients who had Grade 3 SGPT levels during the study, 4 had positive tests for hepatitis B surface antigen, 12 had positive serology for hepatitis C, and another 2 patients were positive for both hepatitis B and hepatitis C. AEs coded as "hepatitis", "liver function tests abnormal", and "SGOT and SGPT increased" resulted in premature discontinuation of study in a total of 6 patients (1 receiving LPV/RTV and 5 receiving ISPI). Although the ISPI treatment group had more patients with extreme SGOT and/or SGPT values, the difference between treatment groups did not reach significance. The proportion of patients receiving LPV/RTV who developed transaminase elevations was slightly higher in this study than in Study M98-863 but similar to that seen in other studies of LPV/RTV in treatment experienced patients. This study supports the earlier finding that patients with documented hepatitis B or hepatitis C are at increased risk for developing transaminase elevations and clinicians should monitor these patients accordingly.

During the study, 5 LPV/RTV patients and 10 ISPI patients developed protocol-defined extreme values of serum amylase (> 2 times the upper limit of normal). Assessing the relationship of increased amylase to LPV/RTV is complicated by the variety of other drugs used in either the LPV/RTV or ISPI regimens. Many patients in each treatment arm received didanosine and/or other NRTIs known to be associated with pancreatitis. Only one ISPI patient required premature discontinuation from study because of elevated amylase and 3 additional patients (2 LPV/RTV and 1 ISPI) had study drug interrupted or dose adjusted. Overall, the frequency of increased amylase in patients receiving LPV/RTV during this study was slightly higher than previously reported for Study M98-863 but was less than that observed in patients receiving ISPI regimens.

EKG Findings

Twelve-lead EKGs were obtained at Baseline and at the Week 24 and Week 48 study visits. They were performed and interpreted by the method standard at each local site and no standardized instructions were given to investigators regarding

the measurement of EKG intervals. Mean heart rate, PR interval, QT interval, and QTc interval were calculated from the reported values for all available data as shown in Table 18. There were no statistically significant changes from Baseline to 24 or 48 weeks in any of the EKG parameters in either treatment group. All mean values in each group were well within the normal range for adults.

Table 18: Mean EKG Parameters at Baseline and Weeks 24 and 48

EKG Parameter* (Mean)	Kaletra Arm	ISPI Arm
Baseline	N=138	N=134
Heart Rate	71.8	70.0
PR Interval	155.6	160.2
QT Interval	371.5	374.0
QTc Interval	400.7	402.3
Week 24	N=111	N=93
Heart Rate	73.1	72.4
PR Interval	154.5	158.0
QT Interval	366.6	370.5
QTc Interval	403.6	402.8
Week 48	N=112	N=67
Heart Rate	71.4	74.1
PR Interval	151.9	153.9
QT Interval	371.5	373.1
QTc Interval	402.4	408.1

*Heart rate expressed in beats/minute. Intervals expressed in msec.

Prolonged PR interval was defined as an interval $\geq$ 210 msec. Three patients, all in the LPV/RTV group, developed prolonged PR interval during the 48 week study period after having normal Baseline measurements. An additional 2 patients (one in each arm) were identified with prolonged PR well after 48 weeks. None of these patients had any documented clinical events suspicious of manifestations of prolonged PR interval.

Eighteen patients (9 in each treatment group) were documented in the database to have a prolonged QTc interval, defined as QTc > 450 msec. Five of these patients had a QTc interval > 450 msec at Baseline. Four patients (2 LPV/RTV and 2 ISPI) were noted to have a QTc interval > 500 msec. In two of these patients there is documentation of prolonged QTc at Baseline. Eleven of the patients with prolonged QTc were noted to have a "changed" EKG over time but in only 4 cases were the changes felt to be clinically significant. Because EKGs were performed infrequently, it was impossible to determine the time to resolution for

the QTc prolongation but in some patients the prolonged interval was identified at Baseline or Week 24 and not present in a later EKG. One of the patients receiving LPV/RTV was noted to have developed prolonged QTc and primary pulmonary hypertension since the time of enrollment. None of these patients developed symptoms suggestive of serious cardiac arrhythmias.

Thirteen AEs coded as CV/Gen or CV/Card were reported in 10 patients enrolled in Study M98-888. Six patients were receiving LPV/RTV and 4 were receiving ISPI at the time of the event. These events were described by the COSTART terms: atrial fibrillation, heart failure, tachycardia, palpitations, angina pectoris, and cardiovascular disease. One patient with angina and one with tachycardia required interruption or dose adjustment of study medications because of the AE but none of the patients prematurely discontinued study.

During the review cycle for this supplement, 2 case reports of bradyarrhythmias were published in the medical literature (see Appendix 1). This prompted a review of the post-marketing safety databases available to both the FDA and to the sponsor in addition to the review of EKG and relevant clinical safety data obtained in Study M98-888. The sponsor provided their additional analysis of cardiac AEs from their full safety database and from their collected post-marketing reports in an amendment to the NDA. After reviewing data from all clinical trials and the Kaletra Early Access Program, the sponsor identified 21 fatal cardiac events in their database. Six of these fatalities occurred either in the lead-in phase of clinical trials or greater than one month after LPV/RTV was discontinued. There did not seem to be a pattern of arrhythmias among the patients suffering fatal events. The sponsor identified 7 patients with syncope, six of whom received LPV/RTV after the event without reported recurrence, one patient with suprventricular tachycardia, and one patient with ventricular tachycardia during LPV/RTV use.

Review of the sponsor's post-marketing safety reports identified 36 reports of cardiac events in patients using LPV/RTV as part of HIV therapy. These included: ventricular arrhythmias and cardiac arrest (11 reports), cardiac conduction disorders (4), supraventricular tachycardia (4), syncope (3), rate disorders (10), EKG changes (2), and palpitations (2). Many of these post-marketing reports provide insufficient detail about the case to make any conclusions regarding a causal relationship to LPV/RTV.

One of the episodes of ventricular arrhythmia was a 40 year old male patient with a history of hepatitis C, cirrhosis and alcohol abuse who experienced a syncopal episode and was found to have torsades de pointes. He was diagnosed with spontaneous bacterial peritonitis at the time and low serum magnesium. LPV/RTV and other medications were stopped and the arrhythmia resolved.

The 4 reports of conduction disorders represent 4 patients who experienced AV block (these include one of the patients described in the CID case report). Two of these patients required pacemaker implantation. The second patient reported in the CID article was a 60 year old male on multiple medications who developed dizziness while taking combination antiretroviral therapy including LPV/RTV. EKG documented sinus arrest with junctional escape.

While there were relatively few cases of cardiac arrhythmias or other clinical events with apparent causal relationship, there were a handful of reports that implicated LPV/RTV as at least a contributing factor. The review team felt that there was sufficient concern to add "bradyarrhythmias" to the list of events reported in the Adverse Reactions, Post-marketing Experience section of the product label. There were no findings from the EKG data obtained in Study M98-888 that warranted precautionary wording in the label.

D. Adequacy of Safety Testing

The safety data collected during Study M98-888 significantly adds to the overall database available for LPV/RTV. This study provides a population of 148 previously treated HIV-infected adults followed over 48 weeks and beyond in comparison to a similar population of patients receiving a variety of other single and dual ISPI regimens. The frequency and variety of safety monitoring were considered appropriate for the class of drug and the population being studied.

E. Summary of Critical Safety Findings and Limitations of Data

LPV/RTV was found to be safe and generally well-tolerated in this population of HIV-infected adults failing single PI therapy. This study did not identify any new, unanticipated toxicity with LPV/RTV at the currently approved dose. The review team confirmed the sponsor's conclusions regarding the frequency of AEs, premature discontinuations, HIV-related events, deaths, and laboratory and EKG abnormalities occurring in patients enrolled in the study. Proportions of patients developing AEs and laboratory toxicity during Study M98-888 were incorporated into the product label in table format.

In this population of HIV-infected adults, as in previously studied groups, the most commonly reported AEs were gastrointestinal events (anorexia, diarrhea, nausea, and vomiting) occurring in up to 45% of patients enrolled. These events have been associated with the use of LPV/RTV and other antiretroviral drugs and the proportions of patients reporting these events were similar to those presented in other studies. There were few identifiable differences between the treatment arms, with slightly more nausea and vomiting of moderate or severe intensity attributed to study drug in patients receiving ISPI regimens. Many of the patients randomized to the ISPI arm received a regimen that included RTV at a dose of 400 mg BID, a dose that is now attributed to higher rates of intolerance.

Evaluation of several specific clinical events occurring during the study identified some numerical differences between treatment arms but none that approached statistical significance. Numerically more patients receiving LPV/RTV developed rashes and more LPV/RTV patients required dose interruption because of rash, although all patients were receiving NVP. All six of the patients reporting "hepatitis" as an AE received ISPI regimens. Four of these patients had documented viral hepatitis and only 2 were thought to have drug related hepatitis or hepatic toxicity. Events fitting the description of body fat composition changes appeared to be evenly distributed across both treatment arms. Similarly, AEs identified as HIV-related conditions, serious AEs, and deaths were balanced across the treatment arms. Compared to the ISPI group, there were fewer patients in the LPV/RTV group who required study drug interruption or dose adjustment.

The major laboratory toxicities associated with LPV/RTV use in Study M98-888 were hypercholesterolemia and hypertryglyceridemia occurring in 20% and 25% of LPV/RTV patients and similar proportions of ISPI patients. This phenomenon has been observed with many of the PIs and was noted during the original NDA review of LPV/RTV. This study confirmed the observation that PI-treatment experienced patients experience higher rates of these lipid abnormalities than treatment naïve patients do. Most of these events were managed medically and did not require premature discontinuation. Other laboratory findings such as elevated amylase, elevated SGOT or SGPT, and hyperglycemia were identified in numerically more patients receiving ISPI regimens. These abnormalities were documented in 1-6% of patients receiving LPV/RTV.

Although an extensive review of EKG data and cardiac events was undertaken during this review cycle, little objective evidence of a causal relationship between LPV/RTV use and cardiac arrhythmias was found. Only 3 patients were found to have prolonged PR interval during the study, none with compatible clinical symptoms. Findings of prolonged QTc interval were identified in 18 patients, evenly distributed between the treatment arms, again without clinical consequences. Review of the post-marketing safety databases available revealed only a few cases of significant arrhythmias that appeared to be associated with LPV/RTV use. After review and internal discussion it was decided that the events of bradyarrhythmias warranted inclusion in the product label.

VIII. Dosing, Regimen, and Administration Issues

The dose selected for use in Study M98-888 was based on an earlier PK study in adults that showed a relatively small change in LPV exposure when the drug was given in combination with NVP and a Phase 2 study of 2 doses of LPV/RTV (Study M97-765 that evaluated 400 LPV/100 RTV and 400 LPV/200 RTV) that suggested higher exposures of LPV did not improve efficacy in a similar population. PK data provided with this

submission and clinical data from another Phase 2 study in treatment experienced patients (Study M98-957) confirmed that the drug interactions between LPV/RTV and NVP are significant and that a dose of 533 mg LPV/133 mg RTV provided a better response rate in treatment experienced patients. The dose of LPV/RTV selected in Study M98-888 provided clearly superior efficacy when compared to the ISPI treatment arm through 48 weeks of dosing. However, it is impossible to know whether response rates would have been even better if the higher dose had been selected for study. Based on the accumulated PK and clinical data, the review team has strengthened the recommendation that a dose of 533 mg LPV/133 mg RTV be used in patients who are receiving concomitant NVP or efavirenz. The review team did not believe that additional data would be needed.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Only 39 of the 288 patients (14%) enrolled in Study M98-888 were female. Response rates in women were numerically lower in both treatment arms (39% in LPV/RTV arm vs. 19% in ISPI arm) than in men (60% in LPV/RTV vs. 35% in ISPI) but the numbers were too small to draw any conclusions. Except for those clinical trials enrolling pregnant women to investigate perinatal transmission of HIV, it has been difficult to enroll adequate numbers of women to evaluate specific drugs or treatment strategies.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

This review also included a Phase 4 commitment analysis requested at the time of approval of a previous efficacy supplement (SE8-005) in Jan, 2002. The sponsor was asked to evaluate the relative treatment response, safety, and tolerability of LPV/RTV in Caucasians vs. Blacks using data from Study M98-888 and all clinical trial data available. The analysis was requested because during the review of Study M98-863 there was a suggestion that Blacks did not respond as well to therapy containing LPV/RTV as Caucasians. The analysis was originally projected to be submitted with the Traditional Approval supplement but was instead submitted as a Clinical Information Amendment to [redacted] 20).

In their analysis, Abbott evaluated adult subjects receiving LPV/RTV in 7 clinical trials as summarized in Table 19. The analysis includes only patients receiving LPV/RTV. There is no corresponding analysis to determine whether the observed differences between Black and Caucasian patients were also observed in the non-LPV/RTV treatment arms. Similar meta-analyses have not been performed for

other antiretroviral drugs so there is no basis for comparison to other current therapy.

Table 19: Patients Included in Efficacy Analysis According to Race

Study	N	Patient Population	Regimen	Subjects Included in Analysis
M97-720	100	ART naïve	LPV/r + d4T/3TC	93
M97-765	70	Single PI experienced	LPV/r + NVP + 2 NRTIs	62
M98-863	326	ART naïve	LPV/r + d4T/3TC	267
M98-888	148	Single PI experienced	LPV/r + NVP + 2 NRTIs	129
M98-957	57	Multiple PI experienced	LPV/r + EFV + NRTIs	53
M99-056	38	ART naïve	LPV/r + d4T/3TC	26
M00-154	44	ART naïve	LPV/r + EFV + TDF + 3TC	39

The efficacy of LPV/RTV in the patients subgrouped according to race are displayed in Table 20. The sponsor chose to stratify their analysis by treatment experience since efficacy rates tend to be significantly higher in treatment naïve patients compared to treatment experienced patients. Their analysis suggests that Black patients across studies have lower therapeutic response rates; this reaches statistical significance for treatment naïve individuals but not for treatment experienced patients.

Table 20: Proportion of Subjects < 400 copies/ml by Race

Population/Analysis	Caucasian	Black	Total
ART Naïve – Week 60			
ITT (NC=F)	215/295 (72.9%)	78/130 (60.0%)*	293/425 (68.9%)
On Treatment	213/233 (91.8%)	74/91 (81.3%)*	287/323 (88.9%)
PI Experienced – Week 48			
ITT (NC=F)	122/193 (63.2%)	27/51 (52.9%)	149/244 (61.1%)
On Treatment	120/155 (77.4%)	27/35 (77.1%)	147/190 (77.4%)

*P-values at the 0.05 level or less.

Efficacy rates in Study M98-888 are similar to those generated for the larger population analysis. In Study M98-888 Caucasian patients receiving LPV/RTV had a Week 48 response rate of 57% while Blacks had a response rate of 50%. Caucasians in the ISPI group had a response rate of 31% compared to 36% in Blacks. There was a smaller treatment difference between the two treatment arms

in Black patients compared to Caucasian patients, however, Black patients receiving LPV/RTV still had higher response rates than those receiving ISPI.

The sponsor suggests that the differences in relative efficacy in the cross-study analysis were explained by differences in patients who discontinued study for reasons other than drug-related or HIV-related adverse events (Caucasians had significantly higher rates of discontinuations attributed to AEs). Black patients had higher rates of discontinuations attributed to "lost to follow up" and "noncompliance" but not to "virologic failure". Also, Blacks had statistically lower adherence than Caucasians in studies in which pill counts were performed, with mean adherence 87% for Blacks vs. 92% for Caucasians. Trough LPV levels were similar for Blacks and Caucasians in Study M98-863, suggesting no inherent difference in drug exposure.

While it appeared that Black patients achieved successful long-term suppression of HIV replication less frequently than did Caucasian patients, it remains unclear whether this is a "real" phenomenon or a function of performing multiple analyses on a relatively small subgroup. Current evidence provides little support for a medical, physiological, or pharmacological difference in treatment response to LPV/RTV. Interpretation of the sponsor's analysis is complicated by the lack of similar meta-analyses of other antiretroviral drugs and the limitations of the meta-analysis (different study populations and trial designs, studies not powered to compare treatment according to race). Finally, although it represents a small sample size, Study M98-888 results suggested that Black patients receiving LPV/RTV had higher response rates over 48 weeks than did those receiving ISPI.

C. 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.

D. Comments on Data Available or Needed in Other Populations

Pharmacokinetic and safety data are still needed to support the use of LPV/RTV in infants younger than 6 months of age. Easily administered formulations of many PIs are still lacking for this age group and LPV/RTV oral solution would be a welcome addition to the HIV armamentarium for young infants. Additional data on the use of higher doses of LPV/RTV in treatment experienced patients, including children, with resistance to other PIs would be useful. The sponsor has initiated clinical trials to investigate some of these issues.

X. Conclusions and Recommendations

A. Conclusions

The results of Study M98-888 comparing LPV/RTV to ISPI in combination with two NRTIs (also investigator selected) and a newly prescribed NNRTI (NVP in this study) confirmed the efficacy of LPV/RTV over 48 weeks of dosing in HIV-infected adults failing single PI-based therapy. This study randomized 288 patients to receive either an LPV/RTV based regimen or an ISPI based regimen (with single or dual PIs). A total of 192 patients completed at least 48 weeks of study. Through 48 weeks, 57% of LPV/RTV patients achieved and maintained an HIV RNA level < 400 copies/ml compared to 33% of ISPI patients. This study extends the population confirmed to benefit from LPV/RTV since it has previously been shown to provide effective therapy for at least 48 weeks in treatment naïve adults in a well controlled Phase 3 trial and in HIV-infected children > 6 months of age. Submission and review of this study completes the sponsor's requirements for Traditional Approval.

Review of the safety data collected on all 288 patients submitted with this supplement identified no new toxicity thought to be related to LPV/RTV. Gastrointestinal adverse events (seen in up to 45% of patients), hypercholesterolemia (in 20%), and hypertriglyceridemia (in 25%) were the most frequently encountered toxicities. These toxicities were also commonly identified in patients receiving ISPI regimens.

Extensive review of EKG data and clinical cardiac events failed to identify any abnormalities that could be clearly attributed to LPV/RTV but a few well-documented post-marketing case reports suggested a temporal association between LPV/RTV use and bradyarrhythmias. Reports of other cardiac events, including the single case of torsades de pointes were not as well-documented or occurred in patients with multiple confounding factors.

B. Recommendations

Based on review of this submission containing 48 week efficacy and safety data for Study M98-888 enrolling previously treated HIV-infected patients and previously reviewed 48 week data from Study M98-863 enrolling treatment naïve patients, Traditional Approval should be granted for LPV/RTV (Kaletra soft gel capsules and oral solution).

Relatively limited changes to the product label were recommended on the basis of this review as described below.

1. The most important change is the addition of a brief description of Study M98-888 and the study outcome to the Description of Clinical Studies section.

Efficacy data has been displayed in both table format (Table 6) and as a Kaplan-Meier plot showing the virologic response through Week 48. Adverse event data for Study M98-888 has been added to Table 10, "Percentage of Patients with Selected Treatment Emergent Adverse Events..." and laboratory data has been added to Table 11, "Grade 3-4 Laboratory Abnormalities Reported in $\geq$ 2% of Adult Patients".

2. The descriptions and results of the Phase 2 studies, Study 720 and Study 765, were consolidated and moved into a briefer section, "Other Studies" at the end of the Description of Clinical Studies section.

3. The PK data confirming the interaction between LPV/RTV and NVP in adult patients has been added to the Drug Interactions in Table 2.

4. In both Table 8, "Established and Other Potentially Significant Drug Interactions..." and in the DOSAGE AND ADMINISTRATION - Adults section, the recommendation has been made to use a dose of 533 mg LPV/133 mg RTV in patients also receiving NVP or efavirenz. Corresponding changes have been made in the Pediatric Patients subsection to recommend the higher dose in children receiving concomitant NVP or efavirenz.

5. The ADVERSE REACTIONS - Post-Marketing Experience section has been revised to include a qualifying statement regarding the limitations of post-marketing reporting and listing "Cardiovascular – bradyarrhythmias" as a reported event.

6. In the INDICATIONS AND USAGE section, the last sentence regarding the lack of controlled trials evaluating the effect of Kaletra on clinical progression of HIV has been deleted.

No additional Phase 4 commitments were requested based on the review of this supplement. The sponsor was reminded of the outstanding Phase 4 commitments requested at the time of previous approval actions.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11-16-02

FROM: Katherine A. Laessig, M.D.
Division of Antiviral Drug Products, HFD-530

TO: Division File

SUBJECT: Group Leader Memo for NDA 21-226 SE7-006, Traditional Approval for KALETRA (lopinavir/ritonavir capsules)

1.0 Background

Kaletra is a formulation of two protease inhibitors: lopinavir and ritonavir. Lopinavir provides the antiviral effect, while ritonavir inhibits the metabolism of lopinavir by the cytochrome p450 enzyme CYP3A, thereby increasing available lopinavir levels. Kaletra capsules and oral solution were approved for the treatment of HIV infection in September 2000, based on substantive evidence of efficacy and safety. This submission contains the 48-week data from a Phase 3 study (888) in treatment experienced adults. A previous efficacy supplement was approved in January 2001 based on 48-week data from studies 940 (pediatric subjects) and 863 (treatment naïve adults).

2.0 Summary of Study Results

Study 888 demonstrates that Kaletra is as safe as, and more effective than, investigator selected protease inhibitor (ISPI) treatment for HIV infected adults with prior nucleoside and single PI treatment experience. The study design was a randomized, open-label, multicenter trial of 288 non-nucleoside reverse transcriptase inhibitor (NNRTI) naïve subjects with a mean baseline viral load of 4.1 $\log_{10}$ copies/ml and mean baseline CD4 count of 322 cells/mm^3. All subjects received 2 NRTIs and nevirapine, as well as either Kaletra or ISPIs consisting of either one or two new PIs as determined by the study investigator. At 48 weeks, results for the Kaletra arm were superior, such that 57% of subjects in the Kaletra arm compared to 33% of subjects in the ISPI arm had a viral load of <400 copies/ml. The mean increase from baseline in CD4 count was similar in the 2 arms: 111 cells/mm^3 for the Kaletra arm, and 112 cells/mm^3 for the ISPI arm.

Rates of adverse events, SAEs, deaths, and clinical laboratory changes were similar for the 2 groups, and not significantly different from rates observed in

previous trials. There were a couple of exceptions, however. Rates of treatment emergent nausea and vomiting were higher in the ISPI arm, particularly in subjects who received dual PI therapy. In addition, the reported AE rate for hyperlipemia was higher for the Kaletra arm, however rates of Grade 3 and 4 hypertriglyceridemia and hypercholesterolemia laboratory changes were similar among the 2 groups.

3.0 Recommendation

The results of study 888 contained in this traditional approval supplement support the safety and efficacy of Kaletra in treatment experienced HIV infected patients, and the inclusion of the 48 week study data in the Description of Clinical Studies and Adverse Reactions section of the label. I concur with the findings of the medical officer review by Dr. Linda Lewis, and recommend that this application should be approved.

Katherine Laessig, MD

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

/s/

Kathrine Laessig
11/27/02 10:06:01 AM
MEDICAL OFFICER

Debra Birnkrant
11/27/02 10:13:28 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-006
21-251 / S-005

STATISTICAL REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Medical Division: **Division of Antiviral Drug Products (HFD-530)**

Biometrics Division: **Division of Biometrics III (HFD-725)**

NEW DRUG APPLICATION (NDA):	21-226
SERIAL NUMBER:	SE7, 006
NAME OF DRUG:	KALETRA™ (lopinavir/ritonavir)
DOSE:	lopinavir 400 mg / ritonavir 100 mg BID (twice a day)
DOSAGE FORM:	lopinavir 133.3 mg/ritonavir 33.3 mg soft gel capsules
INDICATION(S):	Treatment of HIV infection
APPLICANT:	Abbott Laboratories
SUBMISSION DATE:	January 30, 2002
PRESCRIPTION DRUG USER FEE ACT (PDUFA) DATE:	November 29, 2002
DOCUMENTS REVIEWED:	Volumes 1 to 64 (paper copies) file:\\Cdsesub1\N21226\S_006 (electronic data)

STATISTICAL REVIEWER:	Rafia Bhoré, Ph.D. (HFD-725)
STATISTICAL TEAM LEADER:	Greg Soon, Ph.D. (HFD-725)
CLINICAL REVIEWER:	Linda Lewis, M.D. (HFD-530)
PROJECT MANAGER:	Sean Belouin, RPh (HFD-530)

Distribution: HFD-530/Birnkrant
HFD-530/Murray
HFD-530/Laessig
HFD-530/Lewis
HFD-530/Belouin
HFD-725/Bhoré
HFD-725/Soon
HFD-725/Huque
HFD-700/Anello

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

KALETRA™ (lopinavir/ritonavir) is a co-formulation of two Protease Inhibitors—lopinavir (LPV) and ritonavir (RTV)—and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age six months and older. KALETRA (lopinavir/ritonavir) is available as 133.3/33.3 mg oral soft gel capsules and as 80/20 mg/mL oral solution. The currently approved adult dose for KALETRA is 400/100 mg BID and for pediatric patients, the dose is KALETRA 230/57.5 mg/m^2 BID.

KALETRA™ was granted accelerated approval by the FDA on September 15, 2000. In January 2001, the FDA approved additional efficacy labeling claims filed under NDA 21-226, SE8-003 and NDA 21-251, SE8-004 that contained 48-week efficacy data from a Phase III study, M98-863, and 48-week clinical data from a pediatric study, M98-940. Forty-eight week data on Study M98-888 provided in this submission, NDA 21-226, SE7-006 is intended to fulfill the requirements for "*traditional approval*" for KALETRA™.

This submission consists of the final clinical study report on Study M98-888, with data in adults on 48 weeks of treatment and beyond. M98-888 is an open-label, active-control, multinational study in HIV-infected patients failing their first single protease inhibitor (PI)-containing antiretroviral regimen and who had not previously received a non-nucleoside reverse transcriptase inhibitor (NNRTI). The study was designed to compare the safety and antiviral activity of KALETRA against Investigator-selected protease inhibitor(s), both in combination with nevirapine and nucleoside reverse transcriptase inhibitors (NRTIs).

Study 888 enrolled 288 *NNRTI-naïve* patients of age 18 years through 73 years. Majority of the patients were male (86%). Also, the majority of the patients were Caucasian (80%) and the next highest minority was Black patients (18%).

The mean baseline HIV-1 RNA (viral load) was 4.1 $\log_{10}$ copies/ml (approximately 12,760 copies/mL) with a range of 2.6 to 5.98 $\log_{10}$ copies/mL (i.e., 400 to 954,993 copies/mL). The mean baseline CD4+ cell count was about 322 cells/mm^3 with a range of 10 to 1059 cells/mm^3.

Based on all the available data through Week 48 in KALETRA Study M98-888 we conclude the following.

1. Study 888 demonstrated that a statistically significantly higher proportion of patients treated in the KALETRA + nevirapine + NRTIs arm (57%) maintained their viral load <400 copies/mL through Week 48 as compared to those patients treated with Investigator-selected protease inhibitor(s) [ISPIs] + nevirapine + NRTIs (33%). Also, there were significantly lower virologic failures (HIV RNA ≥400 copies/mL) in the KALETRA arm through Week 48 as compared to the Investigator-selected PIs arm.

2. Mean changes from baseline in CD4+ cell count at Week 48 were similar in both treatment groups in Study 888 (about 110 cells/mm^3 at Week 48). However, through 48

weeks of therapy the time-weighted average change from baseline in CD4+ cell count was significantly higher in the KALETRA arm than in the ISPI arm. The mean change from baseline in CD4+ cell count was numerically higher in the KALETRA arm vs. the ISPI arm at every visit through 48 weeks.

3. Among men and women, the proportions of responders through Week 48 were numerically higher in the KALETRA arm than that in the Investigator-selected protease inhibitor(s) arm ([60% vs. 35%] in men and [39% vs. 19%] in women). The treatment difference in men (25%) was similar to that observed in women (20%). These effect sizes were not statistically significantly different, suggesting that the men and women responded similarly to KALETRA.

4. The median age of patients in Study 888 was about 40 years. Based on this cut-off of age, a subgroup analysis evaluating the efficacy of KALETRA was also performed. Significantly higher proportion of patients in the age group 18 years to less than 40 years responded in the KALETRA arm (61%) than in the ISPI arm (28%) with a treatment difference of 33% (95% CI: [17%, 48%]).

   Among patients of age 40 years or greater, the difference in response rates between KALETRA (53%) and Investigator-selected PIs (38%) was only marginally significant. The treatment difference in the older group was 15%, which is only about half as much as that in the younger group (30%). These effect sizes were statistically significantly different (p-value=0.117 < 0.15 for test of interaction) suggesting that there is some evidence that older patients did not respond to KALETRA as well as the younger age group. The proportion of responders, however, was numerically higher in the KALETRA arm in both age groups.

5. Among Caucasian patients, significantly higher proportion of patients in the KALETRA arm responded as compared with the ISPI arm. The response rate in KALETRA treatment arm was 57% (66/115) as compared with 31% (36/115) in the ISPI arm. The treatment difference was 26% (95% CI: [14%, 39%]) and in favor of KALETRA.

   Among the Black patients, this treatment difference was only 14% with a 95% confidence interval of (-13%, 41%) and did not achieve statistical significance (response rate was 50% in KALETRA vs. 36% in ISPI arm). This may have been due to a smaller sample size in the subgroup of Black patients.

   However, the treatment differences in Caucasian patients (26%) and in Black patients (14%) were not statistically significantly different (p-value=0.41). This indicates that there is not enough evidence in Study 888 to show that Black patients respond differently than Caucasian patients.

   In summary, the response rates were numerically higher in KALETRA arm than in the ISPI arm among both Caucasian patients and Black patients. Numbers of patients of other origins were too small to make any conclusions regarding the efficacy of KALETRA.

6. Since Study 888 was open-label, patients and their treating physicians knew which therapy was used. Therefore, it is possible that their decisions in the course of the study may depend on the treatment assigned, thus creating biases. There were two notable imbalances between treatment arms in this study. First is the number of patients who were randomized but never treated (2 in KALETRA vs. 11 in ISPI[s]) and second is the number (proportion) of patients discontinuing the study drug(s) at or prior to Week 48 (36 [24%] in KALETRA versus 60 [43%] in ISPI[s]). It is possible that patients and their treating physicians in the ISPI(s) arm would have more inclination to discontinue therapy prematurely in order to receive KALETRA.

   Some sensitivity analyses incorporating these concerns still showed that the proportion of responders in KALETRA arm is significantly higher than those in the ISPI arm, implying that the efficacy results are fairly robust.

   Another limitation of this study design is the randomization scheme of how patients were either assigned to the KALETRA arm or to the ISPI arm. Due to this a valid comparison of KALETRA versus a single PI or KALETRA versus a dual PI-containing regimen cannot be made. To make such comparisons an alternative design would be as follows. First, the investigator would determine for each patient whether a single PI should be given or a dual PI. Then, in the second step, the patient could be randomized to receive either KALETRA or a single PI in a patient who is supposed to receive a single PI, or to receive either KALETRA or a dual PI in a patient who is supposed to receive a dual PI. Such a design would better facilitate an efficacy comparison between KALETRA (which is a dual PI) and other dual PIs.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

This is a statistical review of the supplemental New Drug Application, NDA 21-226, SE7-006, for KALETRA™ (lopinavir/ritonavir) which is a co-formulation of the protease inhibitor (PI) lopinavir (LPV) boosted by the protease inhibitor ritonavir (RTV).

KALETRA™ was granted *accelerated approval* by the FDA on September 15, 2000. KALETRA™ is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients of age six months and older. In January 2001, the FDA approved additional efficacy labeling claims filed under NDA 21-226, SE8-003 and NDA 21-251, SE8-004 that contained 48-week efficacy data from a Phase III study, M98-863, and 48-week clinical data from a pediatric study, M98-940.

The sponsor, Abbott Laboratories, is now seeking *traditional approval* for KALETRA™ upon review of this submission.

This submission consists of only one study, Study M98-888, with data in adults on 48 weeks of treatment and beyond. M98-888 is an open-label, active-control, multinational study in HIV-infected patients failing their first single PI-containing antiretroviral regimen and who had not previously received a non-nucleoside reverse transcriptase inhibitor (i.e., NNRTI-naïve).

2.2 Data Analyzed and Sources

2.2.1 Study M98-888

Title: "A Randomized, Open-Label, Phase III Study of ABT-378/Ritonavir in Combination with Nevirapine and Two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) vs. Investigator Selected Protease Inhibitor(s) in Combination with Nevirapine and Two NRTIs in Antiretroviral-Experienced HIV-Infected Subjects" [Study Period: May 26, 1999 through September 26, 2001].

The summary below is based on the revised protocol incorporating Administrative Letters No. 1, 2, 3.1 and 4, and Amendments No. 1, 2, 3, 4 and 4.1. The revision date is 08 March 2001. The amended protocol was submitted in Volume 4, page 217 of NDA 21-226, SE7-006.

Study M98-888 was a Phase III, *open-label*, randomized, *positive-controlled*, multi-center, multi-national study in antiretroviral-experienced HIV-infected patients with plasma HIV levels ≥1,000 copies/mL and ≤500,000 copies/mL while treated with a regimen consisting of a protease inhibitor (PI) and 2 NRTIs that had not been changed for

at least 12 weeks. The study was designed to compare the safety and antiviral activity of KALETRA in combination with nevirapine and 2 NRTIs versus Investigator Selected PI (ISPI) (s) in combination with nevirapine and 2 NRTIs in these patients.

Population

The study was conducted by 76 investigators in the USA, Australia, Brazil, Canada, Denmark, France, Germany, Spain, South Africa, Switzerland, and United Kingdom.

Approximately 300 NNRTI-naive subjects at least 12 years of age with plasma HIV RNA levels ≥1000 copies/mL and ≥500,000 copies/mL while treated with a regimen consisting of a single PI and 2 NRTIs that had not been changed for at least 12 weeks were to be enrolled. Patients were randomly assigned either to KALETRA 400 mg/100mg BID or to an ISPI(s) regimen (as shown in Table 1 below). In addition, all subjects received nevirapine and 2 NRTIs selected by the investigator according to protocol-defined guidelines.

Table 1:

Possible Investigator-Selected Protease Inhibitors and their Doses when given with nevirapine in Study M98-888

Single Protease Inhibitor Regimen:	**Dose**
Indinavir (IDV)	1000 mg q8hr
Nelfinavir (NFV)	750 mg TID or 1250 mg BID
Saquinavir (SQV)*	1200 mg TID
Ritonavir (RTV)**	600 mg BID
Dual Protease Inhibitor Regimen:	**Dose**
RTV/SQV	400 mg RTV†,‡ / 400 mg SQV BID
RTV/IDV	400 mg RTV†,‡ / 400 mg IDV BID
NFV/SQV	1250 mg NFV/1200 mg SQV BID or 750 mg NFV/800 mg SQV TID

* Only Fortovase™ can be used for SQV single protease inhibitor regimens.
** Subjects who are assigned to a RTV single protease inhibitor regimen may initiate dosing with RTV as follows: RTV 300 mg BID to start with
†, ‡ See protocol guidelines on dosing RTV with SQV or IDV.

Source: Page 9 of Protocol M98-888 dated 08 March 2001 in Vol. 4, page 239 of NDA 21-226, SE7-006.

The protease inhibitor dosing regimens were to be chosen among those currently in clinical use and after considering the available pharmacokinetic and clinical information for combination therapy with nevirapine

The patients chosen for this study were to be male or female patients of age 12 years or older. Patients should have been NNRTI-naïve with plasma HIV RNA levels ≥1,000 copies/mL and ≤500,000 copies/mL at screening while currently being treated with a regimen consisting of a single PI and 2 NRTIs that had not been changed for at least 12 weeks, have a Karnofsky score greater than or equal to 70, and have at least one NRTI available to which the patient was naïve. Patients who had received prior therapy with a non-nucleoside reverse transcriptase inhibitor (NNRTI) for greater than 7 days or had received treatment with more than one PI concurrently were to be excluded. Patients with abnormal laboratory test results at screening such as hemoglobin <8.0 g/dL, neutrophil count (absolute) <750 cells/μL, platelet count <20,000 per μL, ALT or AST >3xUpper Limit of Normal (ULN), and creatinine >1.5 x ULN, or with vital signs, physical examination and laboratory results that exhibit evidence of acute illness were also to be excluded. Also, patients should not be pregnant or lactating or demonstrate intolerance to nevirapine or receive systemic chemotherapy.

Sample Size

The planned sample size for this study was 150 patients per treatment arm which would provide at least 80% power to detect a 17% difference in the proportion of patients not experiencing a loss of virologic response by Week 48, assuming that 45% and 62% of patients in the two treatment arms are still responding at Week 48. This corresponds to a hazard ratio of 1.67 under the exponential distribution assumption. These power calculations were based on a two-tailed Type I error rate of 0.05, assuming a 20% loss to follow-up by Week 48. The method of Lachin and Foulkes (Biometrics, 1986) was used to estimate the power.

Efficacy Analyses

The primary efficacy variables for the Week 24 and Week 48 analyses were: 1) proportion of subjects with HIV RNA level below 400 copies/mL at Week 24 and 2) time until loss of virologic response through Week 48.

The time of loss of virologic response was defined as the first occurrence of any of the following events, provided the subject had achieved an HIV RNA level below 400 copies/mL by Week 24:

- Two consecutive visits with an HIV RNA level above 400 copies/mL.
- Addition of a new antiretroviral agent, except as permitted by protocol guidelines. (If an adverse event is felt to be primarily related to one of the NRTIs and the investigator believes that this NRTI must be discontinued to allow the subject to remain in the study, the investigator may replace the suspect NRTI with another NRTI that may be better tolerated by the subject. Such a substitution, to the NRTI exchanged, shall be allowed only once for any given subject for the duration of the study.)
- Treatment-related premature discontinuation from the study.

If the final measurement is the first one documenting an increase in HIV RNA level above 400 copies/mL, the time of loss of response will be defined as the time of the final measurement. Those subjects who do not achieve HIV RNA level below 400 copies/mL by Week 24 will have a time of loss of virologic response of Day 1. Subjects whose final HIV RNA measurement precedes Week 48 and is below 400 copies/mL will be considered censored at the time of the final measurement if they have not met any of the criteria for loss of virologic response.

The duration of virologic response through Week 48 will be summarized with a Kaplan-Meier procedure and the log-rank test will be used to evaluate potential treatment differences between the arms. The Kaplan-Meier estimates (and corresponding 95% confidence intervals) of the Week 48 response rates will be computed.

Other secondary efficacy analyses will also be performed as follows:

- Proportion of subjects not experiencing a virologic endpoint by Week 24
- Proportion of subjects with HIV RNA level <400 copies/mL at each time point
- Time until loss of virologic response through Week 24
- Time until HIV RNA nadir
- Time until first HIV RNA level <400 copies/mL
- Change from baseline (to each visit) in HIV RNA level, CD4 cell count, and CD8 cell count
- AUCMB (area under the curve minus baseline) for HIV RNA level, CD4 cell count, and CD8 cell count through Week 16, Week 24 and Week 48.

Plasma HIV RNA levels will be measured by the central laboratory using the Roche Amplicor assay (standard assay with limit of detection=400 HIV RNA copies/mL) at the following time points: Screening, Randomization, Day -1 (Baseline), Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, and every 12 weeks thereafter for study duration and/or termination visit. CD4 cell counts will also be measured at the same post-baseline time points.

All randomized subjects who complete the Day -1/Baseline visit and subsequently take at lease one dose of their assigned antiretroviral regimen or who are lost to follow-up will be included in the efficacy analyses. Randomized subjects with post-baseline measurements who are missing Day -1/Baseline measurements will be included in the efficacy analyses as appropriate.

2.3 Statistical Evaluation of Evidence on Efficacy

2.3.1 Applicant's Results

The applicant's results of efficacy submitted in the NDA were similar to the Statistical Reviewer's results and hence will not be presented here. The Statistical Reviewer's results differed due to the use of the most current definition of the primary endpoint of time-to-loss of virologic response through Week 48, so as to provide consistency across labels of drugs for the treatment of HIV infection. In this section we present the demographics, baseline characteristics and patient disposition through 48 weeks.

2.3.1.1 Demographics and Baseline Characteristics

Table 2 shows the demographics and baseline characteristics of patients in Study 888.

Table 2:

Demographics and Baseline Characteristics in Study M98-888
(Intent-to-Treat population†)

Characteristic		Study M98-888		
		KALETRA™ + nevirapine + 2 NRTIs	Investigator-Selected PI (ISPI) + nevirapine + 2 NRTIs	Total
		n=148	n=140	N=288
Age (years)	Mean (Range)	40.4 (18 to 73)	40.4 (25 to 71)	40.4 (18 to 73)
Weight (kg)	Mean (Range)	74.7 (45 to 116.1)	75.2 (45.3 to 108.9)	75 (45 to 116.1)
Gender	Male	125 (84%)	124 (89%)	249 (86%)
	Female	23 (16%)	16 (11%)	39 (14%)
Race	White	115 (78%)	115 (82%)	230 (80%)
	Black	30 (20%)	22 (16%)	52 (18%)
	Asian /Pacific Islander	1 (1%)	2 (1%)	3 (1%)
	Native American /Alaskan Native	1 (1%)	1 (1%)	2 (1%)
	Mixed Race	1 (1%)	0 (0%)	1 (<1%)
Ethnicity	Hispanic	16 (11%)	21 (15%)	37 (13%)
Baseline HIV RNA (log_{10} copies/mL)	Mean (SD)	4.08 (0.74)	4.13 (0.74)	4.11 (0.75)
	Range	2.6 to 5.78	2.6 to 5.98	2.6 to 5.98
Baseline CD4 count (cells/mm^3)	Mean (SD)	313.2 (175.4)	330.9 (210.8)	322
	Range	22 to 1059	10 to 1017	10 to 1059
Baseline CD8 count (cells/mm^3)	Mean (SD)	939 (449.7)	1017.1 (476.2)	978

Characteristic		Study M98-888		
		KALETRA™ + nevirapine + 2 NRTIs	Investigator-Selected PI (ISPI) + nevirapine + 2 NRTIs	Total
		n=148	n=140	N=288
Prior Antiretroviral therapy				
PIs	amprenavir	3 (2%)	2 (1%)	5 (2%)
	indinavir	66 (45%)	56 (40%)	122 (42%)
	nelfinavir	62 (42%)	62 (44%)	124 (43%)
	ritonavir	13 (9%)	21 (15%)	34 (12%)
	saquinavir/ Invirase	12 (8%)	13 (9%)	25 (9%)
	saquinavir/ Fortovase	12 (8%)	9 (6%)	21 (7%)
NRTIs	abacavir	1 (<1%)	2 (1%)	3 (1%)
	AZT(zidovudine)	100 (68%)	105 (75%)	205 (71%)
	3TC (lamivudine)	99 (67%)	98 (70%)	197 (68%)
	Combivir (AZT+3TC)	35 (24%)	36 (26%)	71 (25%)
	ddI (didanosine)	50 (34%)	55 (40%)	105 (37%)
	d4T (stavudine)	60 (41%)	60 (43%)	120 (42%)
	ddC (zalcitabine)	26 (18%)	21 (15%)	47 (16%)
NNRTIs	efavirenz	1 (<1%)	0 (0%)	1 (<1%)
	nevirapine	0 (0%)	1 (<1%)	1 (<1%)

† Intent-to-treat population is defined as those patients who were randomized and received at least one dose of study drug.

PIs = Protease Inhibitors

NRTIs = Nucleoside reverse transcriptase inhibitors

NNRTIs = Non-nucleoside reverse transcriptase inhibitors

NOTE: Baseline values were defined to be the mean of the last two measurements within 15 days prior to the first dose of study drug.

Source: Table 14.1_4.1, Table 14.1_5.1, Table 14.1_8.1, Table 14.1_9.1, and Table 14.1_10.1 of Study M98-888 Final Report in Vol. 2, Page 017 of NDA 21-226, S-006.

The age of patients in Study 888 ranged from 18 years to 73 years and the median age (not shown in table above) of patients was around 40 years. Majority of the patients were male (86%). Also, the majority of the patients were Caucasian (80%), the next highest minority was Black patients (18%), and the remaining 2% patients were of other origins.

The mean baseline HIV-1 RNA (viral load) was 4.1 $\log_{10}$ copies/ml (approximately 12,760 copies/mL) with a range of 2.6 to 5.98 $\log_{10}$ copies/mL (i.e., 400 to 954,993 copies/mL). The mean baseline CD4+ cell count was about 322 cells/mm^3 with a range

of 10 to 1059 cells/mm^3.

In Study 888, patients had previously received a single protease inhibitor-containing regimen among which the most commonly used PIs were indinavir (42%) and nelfinavir (43%). Almost all of the patients were NNRTI-naïve with the exception of 2 patients who had previously received efavirenz or nevirapine.

2.3.1.2 Patient Disposition

Table 3 shows the disposition of patients through 48 weeks in Study 888.

Table 3: Patient Disposition through 48 weeks
in KALETRA™ Study M98-888

Number of Subjects	KALETRA™ + nevirapine + 2 NRTIs	Investigator-Selected PI (ISPI) + nevirapine + 2 NRTIs	Total
Total Randomized	150	151	301
Randomized but not treated †	2	11	13
Treated (ITT) ‡	**148**	**140**	**288**
Completed study through Week 48	**112 (76%)**	**80 (57%)**	**192 (67%)**
Discontinued study at or prior to Week 48	**36 (24%)**	**60 (43%)**	**96 (33%)**
Reason discontinued			
Adverse event / HIV related event	8 (5%)	19 (14%)	27 (9%)
Death	1 (<1%)	3 (2%)	4 (1%)
Lost to follow-up	3 (2%)	7 (5%)	10 (3%)
Non-compliance	6 (4%)	6 (4%)	12 (4%)
Personal reasons	4 (3%)	5 (4%)	9 (3%)
Protocol violation	1 (<1%)	0 (0%)	1 (<1%)
Virologic failure	3 (2%)	18 (13%)	21 (7%)
Other §	9 (6%)	2 (1%)	11 (4%)

Percentages in the table are calculated based on the total number of treated subjects in each group.
† Randomized-but-not-treated patients were randomized but did not receive any study medication.
‡ Treated patients were randomized and received at least one dose of study medication. This is also the intent-to-treat (ITT) population.
§ Other category includes other reasons only.

Source: Table 14.1_2.1 and Table 14.1_3.1 of Study M98-888 Report in Vol. 2, Page 017.

Statistical Reviewer's Comments:

Recall that Study 888 was an open-label study where KALETRA was compared with any

investigator-selected protease inhibitor(s) [ISPI], either single PI or dual PI. Note that due to the open-label design, a patient who is randomized to either treatment arm will know which drug they will be receiving and can subsequently decide to continue to be treated or not to be treated. In the KALETRA arm, only 2 patients were randomized but not treated while in the investigator-selected PI arm 11 patients were randomized but not treated. This could bias the efficacy results in favor of KALETRA. A sensitivity analysis will be discussed later to account for this imbalance.

A total of one-third patients (33%) discontinued the study at or prior to Week 48. A greater proportion of patients in the KALETRA arm completed the study through 48 weeks (76%) as compared with the control arm of ISPI (57%). A higher proportion of patients discontinued due to an adverse event in the ISPI arm (14%) as compared with the KALETRA arm (5%).

As will be shown in Section 2.3.2.1, the efficacy of KALETRA compared with the ISPIs will be evaluated while accounting for the various reasons of discontinuation.

Table 4:

Summary of Treatment Regimens for Patients in the Investigator-Selected Protease Inhibitor (PI) Group

Regimen	Number of Patients (N=140) n (%)
Single Protease Inhibitor	41 (29%)
Nelfinavir	29 (21%)
Indinavir	8 (6%)
Ritonavir	3 (2%)
Saquinavir	1 (<1%)
Dual Protease Inhibitors	99 (71%)
Ritonavir/Saquinavir	62 (44%)
Ritonavir/Indinavir	29 (21%)
Saquinavir/Amprenavir	1 (<1%)
Saquinavir/Nelfinavir	7 (5%)

Source: Table 14.1_1.2 of Study M98-888 report in Vol.2, Page 005.

Table 4 shows a summary of protease inhibitors that were selected by the investigators for patients who were randomized to the control arm. About 29% of the patients in the control arm were given a single protease inhibitor while majority of the rest (71%) received dual protease inhibitors. Recall that KALETRA is a co-formulation of two protease inhibitors; lopinavir boosted by ritonavir.

2.3.2 Statistical Reviewer's Findings on Efficacy

In Study 888, plasma HIV-1 RNA was measured by the standard assay, namely, the Roche Amplicor HIV-1 Monitor Test (Standard, LOD=400 copies/mL) at screening, pre-baseline, baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24 and every 8 weeks thereafter.

The standard assay will be used for the primary efficacy analysis and will be the focus of this review. In addition, CD4 results will also be discussed.

Subgroup efficacy analyses based on the demographics, such as age, gender and race are also discussed.

2.3.2.1 Plasma HIV-1 RNA with Standard Assay (LOD=400 copies/mL)

The primary efficacy endpoint for Study 888 for the 48-week data was the durability of the antiviral response, defined as the *time to loss of virologic response* through Week 48.

Although the applicant had proposed an algorithm for computing the *time to loss of virologic response* through Week 48 in the protocol, the following algorithm as defined by the Division of Antiviral Drug Products (DAVDP)/FDA, was used to perform the final efficacy analyses and present the results in the KALETRA label. This algorithm has been used to determine the "success" status of patients at any visit and to compute the time to event (i.e., loss-of-virologic response) because not all visits occur as scheduled and sometimes there are multiple evaluations for a given visit. The FDA algorithm will appear in the updated version of a Guidance for Industry (Clinical considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA Measurements).

According to this algorithm if a patient is suppressed virologically without discontinuing therapy, then the patient is classified as a success regardless of whether a CDC Class C event occurred or not. In this algorithm, failures are carried forward.

Time to Loss-of-Virologic-Response Algorithm (defined by DAVDP/FDA)

For NDAs with 48-week virologic data, one analysis for computing time to virologic failure may be assessed using the following algorithm.

1. In what follows, visit means visit with an observed viral load. All available visits, including off-schedule visits and post Week 48 visits, should be used for the calculation. Data should not be interpolated for visits or time points with missing data.

2. Subjects who never achieved confirmed HIV RNA levels below the assay limit (on two consecutive visits) before any of the following events will be considered to have failed at time 0.

   a) Death

   b) Discontinuation or switching of study medications. Temporary

discontinuation or dose reduction of study medications may be ignored. Discontinuation or dose reduction of background therapies in blinded studies can be ignored. The handling of other changes in background therapies should be pre-specified in the protocol and discussed with the division.

c) Last available visit

3. For all subjects who have confirmed HIV RNA levels below an assay limit, the time to failure is the earliest of the choices below, with modification specified in 4.

a) Time of the event as described in 2b

b) Time of loss to follow-up

c) Time of confirmed levels above an assay limit. Confirmed is define as two consecutive levels greater than an assay limit or one visit greater than an assay limit followed by loss to follow-up.

d) Time of death.

4. If the time to virologic failure defined above is immediately preceded by a single missing scheduled visit or multiple consecutive missing scheduled visits, then the time of virologic failure is replaced by the time of the first such missing visit.

For open-label studies, algorithms that incorporate other ways of handling missing data or treatment discontinuations may be used for additional sensitivity analyses. For example, sponsors should perform analyses that treat nonprotocol-specified treatment discontinuations as failures in the study arm and as censored at the time of discontinuation in the control arm when exploring sensitivity of the results to potential biases related to an open-label design.

Based on the algorithm above, the Week 48 virological responses and status of subjects are summarized.

Table 5 shows the proportion of patients who were virologically suppressed (<400 copies/mL) through Week 48 in Study 863.

Table 5:
Proportion of Patients with HIV-1 RNA <400 copies/mL through Week 48
(Study M98-888)†

	Study 888	
	Treatment Group	
	KALETRA™ + nevirapine + 2 NRTIs (N=148)	Investigator-selected PI + nevirapine + 2 NRTIs (N=140)
Number (%) of successes (plasma HIV-1 RNA <400 copies/mL)	84 (57%)	46 (33%)
p-value or treatment difference (95% CI)	<0.001‡ 24% (12.1%, 34.4%)	

Percentages calculated are based on the number of randomized subjects in each group.
Results are based on the Standard Assay.
† Scenario: Time to loss-of-virologic response-algorithm.
‡ P-value comparing treatment groups is based on Pearson's chi-square test.

Source: FDA Statistical Reviewer's analysis

Failures were due to virologic failure (viral load ≥400 copies/mL) or due to discontinuation of randomized treatment. Table 6 below shows the status of these subjects at Week 48 in Study 888.

Table 6:

Efficacy Outcomes of Randomized Treatment through Week 48
in Antiretroviral-Experienced HIV-Infected Patients
(Study M98-888)

Outcome	KALETRA + nevirapine + 2 NRTIs (N=148)	Investigator Selected PI + nevirapine + 2 NRTIs (N=140)
	n (%)	n (%)
Responder*[1]	**84 (57%)**	**46 (33%)**
Virologic Failure[2]	**35 (24%)**	**58 (41%)**
Rebound	16 (11%)	26 (19%)
Never suppressed through Week 48	19 (13%)	32 (23%)
Death	**1 (1%)**	**3 (2%)**
Discontinued due to adverse events	**7 (5%)**	**15 (11%)**
Discontinued due to other reasons[3]	**21 (14%)**	**18 (13%)**
Consent withdrawn (Personal reasons)	3 (2%)	5 (4%)
Loss to follow	2 (1%)	7 (5%)
Non-compliance	5 (3%)	4 (3%)
Protocol violation (Required prohibited medication)	2 (1%)	0 (0%)
Other	9 (6%)	2 (1%)
Total	**148 (100%)**	**140 (100%)**

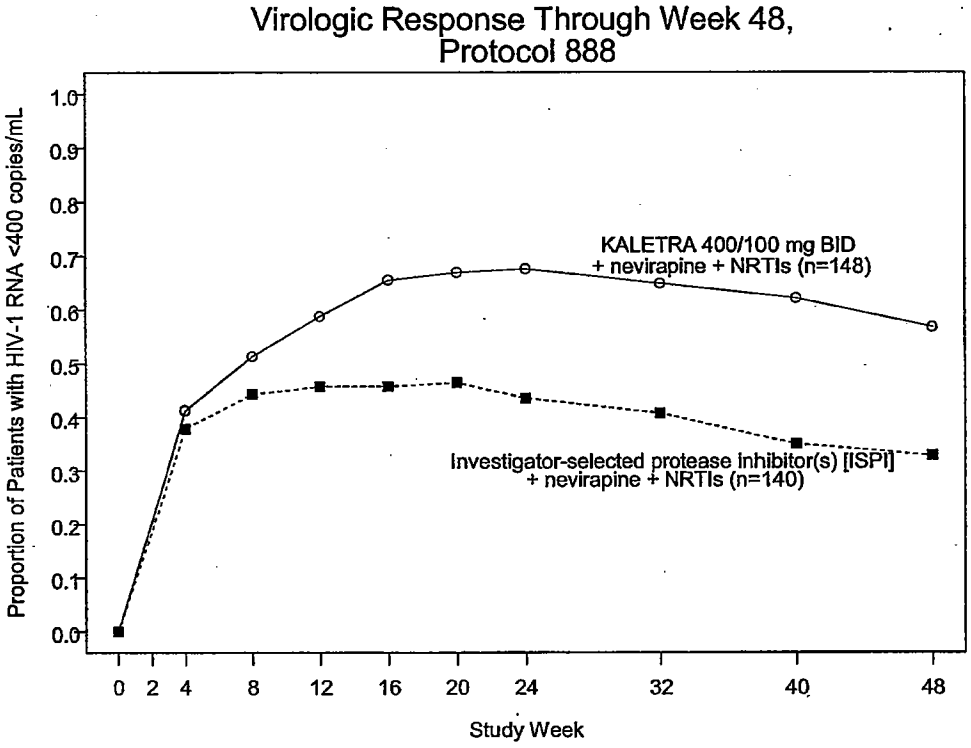
* Corresponds to rates at Week 48 in Figure 1.
NOTE: A total of 301 patients were enrolled in Study M98-88 out of which 288 patients were randomized and received at least one dose (ITT population) and 13 were never treated.
1 Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.
2 Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
3 Includes loss to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.
Source: FDA Statistical Reviewer's analysis.

In Study 888, the proportion of patients with HIV-1 RNA <400 copies/mL in the KALETRA arm (57%) was statistically significantly higher than that in the Investigator-selected PI arm (33%). Also, the proportion of patients with HIV-1 RNA ≥400 copies/mL in the KALETRA arm (24%) was lower than that in the Investigator-selected PI arm (41%).

The remaining failures were due to discontinuations of randomized treatment and death. The proportions of discontinuations due to other reasons were similar in both treatment arms. The efficacy outcome was attributed to death in 4 patients (1 in KALETRA arm [Patient ID 8162] and 3 in Investigator-selected PI arm [Patient Ids 8044, 8016, and 8098]). Additionally, two patients died, but their efficacy outcome was attributed to either discontinuation due to adverse event (Patient ID 8038 in KALETRA arm) or due to

virologic rebound (Patient ID 8107 in ISPI arm) because these events occurred prior to the patient's demise. This classification was based on the time-to-loss of virologic response algorithm.

Figure 1 shows the proportion of successes (<400 copies/mL) at each time point through Week 48 for the KALETRA and Investigator-selected PI arms.



Source: FDA Statistical Reviewer's analysis.

Figure 1: Proportion of Patients with HIV-1 RNA <400 copies/mL through Week 48 (KALETRA Study M98-888)

Sensitivity analyses were also performed to evaluate the robustness of the efficacy results because Study 888 was an open-label trial that could give favorable efficacy results for KALETRA. There were two concerns with the open-label design that create imbalance across treatment arms: 1) patients who were randomized but never took the study treatment (2 in KALETRA vs. 11 in ISPI arm), and 2) patients who prematurely discontinued treatment (7+21=28 in KALETRA vs. 15+18=33 in ISPI arm as shown in Table 6).

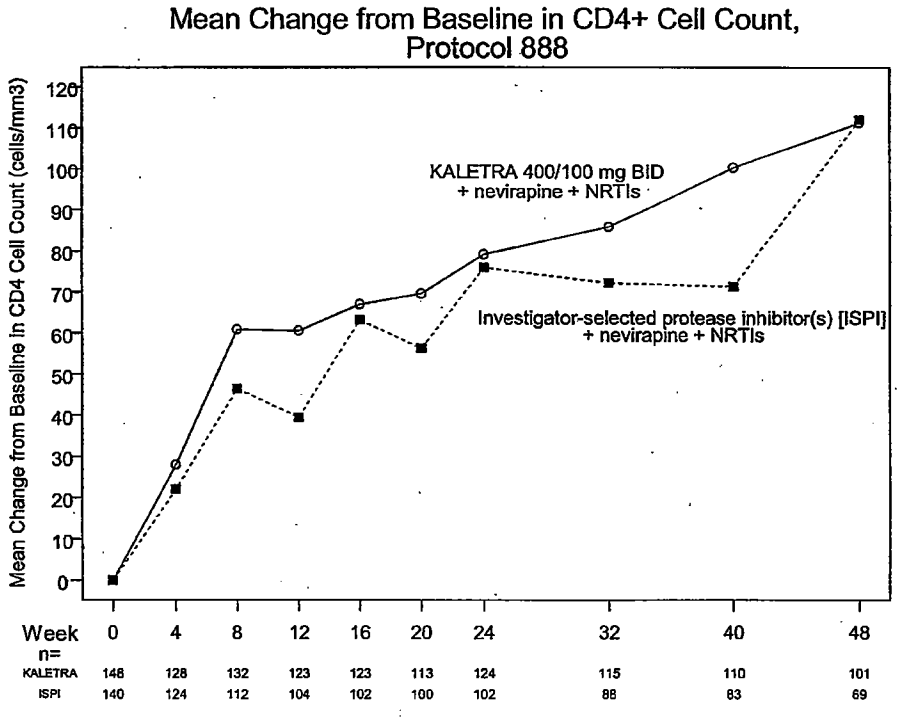
In one scenario, a conservative approach is to ignore the 2 patients who were randomized to KALETRA but not treated, but consider the 11 patients in the control arm (ISPI) as successes. Accordingly, the proportion of responders in the KALETRA arm would be

84/148=57% and in the ISPI arm would be (46+11=)57/151=38%. This treatment effect of 19% (95% CI; [7.2%, 29.5%]) is statistically significant (p-value=0.001). Another approach is to remove from the denominator, the 33 patients who discontinued in the ISPI arm, but still consider the response rate in KALETRA arm to be 84/148=57%. The response rate in ISPI arm would then be 46/(140-33)=46/107=43% and the treatment difference will be 14% (95% CI; [0.6%, 25.3%]) with a p-value=0.039 which is also statistically significant.

These analyses indicate that the efficacy results are fairly robust and are in favor of KALETRA.

2.3.2.2 CD4+ Cell Count

Figure 2 shows the trend in the mean change from baseline in CD4+ cell counts (cells/mm3) in Study 888. At Week 48, the mean increase in CD4+ cell count in both treatment groups was about 110 cells/mm^3.



Source: FDA Statistical Reviewer's graph based on data in Table 14.2_5.1 in Vol. 2, Page 123 of NDA.

Figure 2: Mean Change from Baseline in CD4+ Cell Count through Week 48 (KALETRA Study M98-888)

Although, the increase in CD4+ cell counts from baseline was not statistically

significantly different between KALETRA and Investigator-selected PI arms at each visit up to Week 48, the increase in CD4+ cell counts were numerically higher in the KALETRA arm at every visit. Therefore, we looked at the time-weighted average change from baseline (AUCMB) at Weeks 16, 24, and 48 (i.e., $DAVG_{16}$, $DAVG_{24}$, and $DAVG_{48}$. At Week 48, the *time-weighted average change from baseline* in CD4+ cell count was significantly higher in the KALETRA arm ($DAVG_{48}$ = 64.0, SE=6.81, n=147) than in the ISPI arm ($DAVG_{48}$ = 48.9, SE=6.98, n=140). This suggests that through 48 weeks of therapy, patients responded more favorably to KALETRA than ISPIs in terms of increases in CD4 cell counts from baseline.

2.4 Findings in Special/Subgroup Populations

Table 7, Table 8, and Table 9 show subgroups analyses (response rates) for KALETRA and Investigator-selected PIs by gender, age and race respectively, for Study 888. Since the median age of patients in Study 888 was about 40 years, the age groups were split into 18 to <40 years and >=40 years.

Table 7:
Proportion of Patients with HIV-1 RNA <400 copies/mL through Week 48 by Gender (Study M98-888)†

	KALETRA +NVP+NRTIs (N=148)	ISPI +NVP+NRTIs (N=140)	Treatment Difference (95% CI)	p-value
Male	75/125 (60%)	43/124 (35%)	25% (13.3%, 36.3%)	<0.001*
Female	9/23 (39%)	3/16 (19%)	20% (-7.3%, 48.0%)	0.148
Difference in treatment differences (Treatment by Gender interaction)			5% (-25.2%, 35.1%)	0.748

95% CI = 95% Confidence interval
P-value is based on chi-square test.
† Based on time to loss of virologic response algorithm.
* P-value is statistically significant.

Source: FDA Statistical Reviewer's analysis.

Table 8:
Proportion of Patients with HIV-1 RNA <400 copies/mL through Week 48 by Age (Study M98-888)†

	KALETRA +NVP+NRTIs (N=148)	ISPI +NVP+NRTIs (N=140)	Treatment Difference (95% CI)	p-value
18 to <40 years	43/71 (61%)	20/72 (28%)	33% (17.4%, 48.2%)	<0.001*
>=40 years	41/77 (53%)	26/68 (38%)	15% (-1.0%, 31.1%)	0.067
Difference in treatment differences (Treatment by Age interaction)			18% (-4.4%, 40%)	0.117

95% CI = 95% Confidence interval
P-value is based on chi-square test.
† Based on time to loss of virologic response algorithm.
* P-value is statistically significant.

Source: FDA Statistical Reviewer's analysis.

For male and female patients, as well as for patients in either age groups (≤ 40 years or >40 years), the proportion of responders were numerically higher in the KALETRA arm than in that in the investigator-selected protease inhibitor(s) arm.

Recall that the number of female patients (only 14%) in the study were fewer than male patients (86%). Therefore perhaps due to a smaller sample size, statistical significance between the treatment groups in the subgroup of female patients was not observed. However, a higher proportion of women in the KALETRA arm were responders (39%=9/23) than in the ISPI arm (19%=3/16). The treatment differences between KALETRA and ISPIs were similar among men and women (p-value=0.748), and were numerically in favor of KALETRA.

Significantly higher proportion of patients in the age group 18 years to <40 years responded in the KALETRA arm (61%) than in the ISPI arm (28%). (See Table 8.) The treatment difference between KALETRA (53%) and the ISPIs (38%) was only marginally significant among the age subgroup of >=40 years (p-value=0.067). Note that the sample sizes were similar and sufficiently large in all the age subgroups.

The treatment difference in the older group was 15%, which is only about half as much as that in the younger group (30%). These effect sizes were statistically significantly different (p-value=0.117 < 0.15 for test of interaction) suggesting that there is some evidence that older patients did not respond to KALETRA as well as the younger age group. The proportion of responders, however, was numerically higher in the KALETRA arm in both age groups.

Table 9:
Proportion of Patients with HIV-1 RNA <400 copies/mL through Week 48 by Race (Study M98-888)†

	KALETRA +NVP+NRTIs (N=148)	ISPI +NVP+NRTIs (N=140)	Treatment Difference (95% CI)	p-value
Caucasian	66/115 (57%)	36/115 (31%)	26% (13.7%, 38.5%)	<0.001*
Black	15/30 (50%)	8/22 (36%)	14% (-13.3%, 40.5%)	0.321
Asian/Pacific Islander	1/1 (100%)	1/2 (50%)		
Native American /Alaskan Native	2/2 (100%)	1/1 (100%)		
Difference in treatment differences (Caucasian vs. Black) (Treatment by Race interaction)			12% (-17.2%, 42.1%)	0.410

95% CI = 95% Confidence interval
P-value is based on chi-square test.
† Based on time to loss of virologic response algorithm.
* P-value is statistically significant.

Source: FDA Statistical Reviewer's analysis.

A subgroup analysis by race on the efficacy of KALETRA compared with Investigator-selected protease inhibitors was also performed as seen in Table 9. The numbers of patients of Asian/Pacific Island or Native American/Alaskan Native origin were very small to make any meaningful comparisons between the two treatment groups. Recall that the majority of patients in Study 888 were Caucasian (80%) and the next highest minority was Black patients.

Among Caucasian patients, significantly higher proportion of patients in the KALETRA arm responded as compared with the ISPI arm. The response rate in KALETRA treatment arm was 57% (66/115) as compared with 31% (36/115) in the ISPI arm. The treatment difference was 26% with a 95% confidence interval of (14%, 39%). However, among the Black patients, this treatment difference was only 14% with a 95% confidence interval of (-13%, 41%) and did not achieve statistical significance. This may have been due to a smaller sample size in the subgroup of Black patients. Note that the response rates were numerically higher in KALETRA arm than in the ISPI arm among both Caucasian patients and Black patients.

However, the treatment differences in Caucasian patients (26%) and in Black patients (14%) were not statistically significantly different (p-value=0.41). This indicates that there is not enough evidence in Study 888 to show that Black patients respond differently than Caucasian patients.

In summary, the response rates were numerically higher in KALETRA arm than in the ISPI arm among both Caucasian and Black patients. Numbers of patients of other origins were too small to make any conclusions regarding the efficacy of KALETRA.

3. CONCLUSIONS AND RECOMMENDATIONS

Based on all the available data through Week 48 in KALETRA Study M98-888 we conclude the following.

1. Study 888 demonstrated that a statistically significantly higher proportion of patients treated in the KALETRA + nevirapine + NRTIs arm (57%) maintained their viral load <400 copies/mL through Week 48 as compared to those patients treated with Investigator-selected protease inhibitor(s) [ISPIs] + nevirapine + NRTIs (33%). Also, there were significantly lower virologic failures (HIV RNA ≥400 copies/mL) in the KALETRA arm through Week 48 as compared to the Investigator-selected PIs arm.

2. Mean changes from baseline in CD4+ cell count at Week 48 were similar in both treatment groups in Study 888 (about 110 cells/mm^3 at Week 48). However, through 48 weeks of therapy the time-weighted average change from baseline in CD4+ cell count was significantly higher in the KALETRA arm than in the ISPI arm. The mean change from baseline in CD4+ cell count was numerically higher in the KALETRA arm vs. the ISPI arm at every visit through 48 weeks.

3. Among men and women, the proportions of responders through Week 48 were numerically higher in the KALETRA arm than that in the Investigator-selected protease inhibitor(s) arm ([60% vs. 35%] in men and [39% vs. 19%] in women). The treatment difference in men (25%) was similar to that observed in women (20%). These effect sizes were not statistically significantly different, suggesting that the men and women responded similarly to KALETRA.

4. The median age of patients in Study 888 was about 40 years. Based on this cut-off of age, a subgroup analysis evaluating the efficacy of KALETRA was also performed. Significantly higher proportion of patients in the age group 18 years to less than 40 years responded in the KALETRA arm (61%) than in the ISPI arm (28%) with a treatment difference of 33% (95% CI: [17%, 48%]).

   Among patients of age 40 years or greater, the difference in response rates between KALETRA (53%) and Investigator-selected PIs (38%) was only marginally significant. The treatment difference in the older group was 15%, which is only about half as much as that in the younger group (30%). These effect sizes were statistically significantly different (p-value=0.117 < 0.15 for test of interaction) suggesting that there is some evidence that older patients did not respond to KALETRA as well as the younger age group. It may be possible that older patients had longer duration of prior antiretroviral therapy. The effect of prior duration of antiretroviral therapy on efficacy of KALETRA was not further evaluated. The proportion of responders, however, was numerically higher in the KALETRA arm in both age groups.

5. Among Caucasian patients, significantly higher proportion of patients in the KALETRA arm responded as compared with the ISPI arm. The response rate in KALETRA

treatment arm was 57% (66/115) as compared with 31% (36/115) in the ISPI arm. The treatment difference was 26% (95% CI: [14%, 39%]) and in favor of KALETRA.

Among the Black patients, this treatment difference was only 14% with a 95% confidence interval of (-13%, 41%) and did not achieve statistical significance (response rate was 50% in KALETRA vs. 36% in ISPI arm). This may have been due to a smaller sample size in the subgroup of Black patients.

However, the treatment differences in Caucasian patients (26%) and in Black patients (14%) were not statistically significantly different (p-value=0.41). This indicates that there is not enough evidence in Study 888 to show that Black patients respond differently than Caucasian patients.

In summary, the response rates were numerically higher in KALETRA arm than in the ISPI arm among both Caucasian patients and Black patients. Numbers of patients of other origins were too small to make any conclusions regarding the efficacy of KALETRA.

6. Since Study 888 was open-label, patients and their treating physicians knew which therapy was used. Therefore, it is possible that their decisions in the course of the study may depend on the treatment assigned, thus creating biases. There were two notable imbalances between treatment arms in this study. First is the number of patients who were randomized but never treated (2 in KALETRA vs. 11 in ISPI[s]) and second is the number (proportion) of patients discontinuing the study drug(s) at or prior to Week 48 (36 [24%] in KALETRA versus 60 [43%] in ISPI[s]). It is possible that patients and their treating physicians in the ISPI(s) arm would have more inclination to discontinue therapy prematurely in order to receive KALETRA.

   Some sensitivity analyses incorporating these concerns still showed that the proportion of responders in KALETRA arm is significantly higher than those in the ISPI arm, implying that the efficacy results are fairly robust.

   Another limitation of this study design is the randomization scheme of how patients were either assigned to the KALETRA arm or to the ISPI arm. Due to this a valid comparison of KALETRA versus a single PI or a dual PI-containing regimen cannot be made. To make such a comparison an alternative design would be as follows. First, the investigator would determine for each patient whether a single PI should be given or a dual PI. Then, in the second step, the patient could be randomized to receive either KALETRA or a single PI in a patient who is supposed to receive a single PI, or to receive either KALETRA or a dual PI in a patient who is supposed to receive a dual PI. Such a design would better facilitate an efficacy comparison between KALETRA and dual PIs.

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/s/

Rafia Bhore
11/27/02 10:39:01 AM
BIOMETRICS

Greg Soon
11/27/02 01:51:26 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226 / S-006
21-251 / S-005

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, Illinois 60064-6157

October 18, 2002

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, Maryland 20855-2773

Re: KALETRA
Abbott-157378.0 (ABT-378)
NDA 21-226

GENERAL CORRESPONDENCE
TIME SENSITIVE PATENT INFORMATION

Dear Sir/Madam:

Reference is made to our approved New Drug Application, 21-226 for Kaletra (lopinavir/ritonavir) Capsules. At this time we wish to submit this application with the following new patent information as allowed per CFR 314.53(c)(2)(ii). The sponsor, Abbott Laboratories, certifies that no previous patents claim this drug product formulation.

United States Patent No. 6,458,818 was issued on October 1, 2002. This patent has claims encompassing the composition of lopinavir/ritonavir as it is presently marketed for Kaletra Capsules.

U.S. Patent #	6,458,818
Name of Patent Owner	Abbott Laboratories
Type of Patent	Drug Product
Expiration Date	November 7, 2017

Previously, the following patents have been filed under NDA 21-226:

Submitted on 10/16/00	Submitted on 6/7/01	Submitted on 9/12/01
#5,914,332	#6,232,333	#6,284,767
#5,635,523		
#5,846,987		
#5,674,882		
#5,886,036		
#6,037,157		
#5,541,206		
#5,648,497		

A Patent Declaration is attached. At this same time, a copy of this correspondence will be sent to the Division of Antiviral Drug Products.

As provided by 21 CFR 314.53(e), the sponsor is requesting this patent information be published in the next supplement to the Orange Book list. In addition, we understand that this patent information will be placed on public display in the FDA Freedom of Information Staff Office.

If you have any questions regarding this submission, or if you need any additional information, please feel free to contact me at the number listed below. Thank you for your consideration in this matter.

Sincerely,

Greg Bosco

Greg Bosco
Associate Director
PPD Regulatory Affairs
(847) 937-6970

Declaration of Patent

The undersigned declares that the following patent covers the composition of Kaletra Capsules, NDA 21-226 and that Kaletra is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act.

Patent #	Expiration Date	Topic of Patent
6,458,818	Nov 7, 2017	Drug product

pharmaceutical composition comprising both lopinavir and ritonavir

The sponsor, Abbott Laboratories, certifies that no previous patents claim this drug product formulation.

Greg Bosco 10/18/02

Greg Bosco
Associate Director
PPD Regulatory Affairs
Abbott Laboratories
(847) 937-6970

Date

Declaration of Patent

The undersigned declares that the following patent covers the compound for ABT-378 .

Patent #	Expiration Date	Topic of Patent
5,914,332	December 13, 2015	Compound

The sponsor, Abbott Laboratories, certifies that no previous patents claim this drug formulation.

Rebecca A. Welch
Associate Director
PPD Regulatory Affairs
Abbott Laboratories

Reference is made to New Drug Application 21-226, ABT-378 (lopinavir) Capsules. At this time we wish to include in this application the following patent information as allowed per CFR 314.53(a). The sponsor, Abbott Laboratories, certifies that no previous patents claim this compound.

United States Patent No. 5,914,332 was issued on June 22, 1999. This patent claims the compound.

Patent #	5,914,332
Name of Patent Owner	Abbott Laboratories
Type of Patent	Compound
Expiration Date	December 13, 2015

A Patent Declaration is attached. A copy of this information will also be sent to the FDA Drug Information Services.

As provided by 21 CFR 314.53(e), the sponsor is requesting this patent information be published in the next supplement to the Orange Book list. In addition, we understand that this patent information will be placed on public display in the FDA Freedom of Information Staff Office.

EXCLUSIVITY SUMMARY for NDA # 21-226 & 21-251 SUPPL # 006 & 005

Trade Name Kaletra® Generic Name lopinavir/ritonavir

Applicant Name Abbott Laboratories HFD-530

Approval Date November 27, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /X/

   b) Is it an effectiveness supplement? YES /X/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-7

   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 YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA # 21-226 & 21-251 Drug Name Kaletra Capsules & Kaletra Oral Solution

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /___/ 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 9:**

_____

_____

(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 /___/

(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 /___/

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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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 /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ 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 /___/

If yes, explain: _____

_____

_____

Signature of Preparer
Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

October 31, 2002
Date

Signature of Office or Division Director
Debra Birnkrant, M.D.
Division Director
Division of Antiviral Drug Products

11/27/02
Date

cc:
Archival NDA 21-226/S-006 & NDA 21-251/S-005
HFD-530/Division File
HFD-530/RPM/Belouin
HFD-530/CRPM/DeCicco
HFD-530/DivDir/Birnkrant
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Debra Birnkrant
11/27/02 10:22:30 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA# : 21-226 & 21-251 Supplement Type (e.g. SE5): SE-7 Supplement Numbers: 006 & 005

Stamp Date: January 30, 2002 Action Date: November 26, 2002

HFD-530 Trade and generic names/dosage form: Kaletra® (lopinavir/ritonavir) Capsules and Oral Solution

Applicant: Abbott Laboratories Therapeutic Class: Antiviral Agent, Protease Inhibitor

Indication(s) previously approved: KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of KALETRA of 48 weeks duration and in smaller uncontrolled dose-ranging studies of KALETRA of 72 weeks duration. At present, there are no results from controlled trials evaluating the effect of KALETRA on clinical progression of HIV.

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

Number of indications for this application(s): One

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

☐ Yes: Please proceed to Section A.

☒ No: Please check all that apply:

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: Not Applicable

☐ 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: Not Applicable

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver: Not Applicable

- ☐ 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: 2 age ranges deferred.

mo._

yr.

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:

mo

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}

Sean J. Belouin, R.Ph
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Sean Belouin
11/27/02 10:06:49 AM

Kathrine Laessig
11/27/02 10:13:28 AM

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)].

Rebecca A Welch

3/31/00

Rebecca A. Welch
Associate Director, PPD Regulatory Affairs
Abbott Laboratories
Dept. 491, Bldg. AP6B-1
(847) 937-8971
100 Abbott Park Road
Abbott Park, Illinois 60064-6108