DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21251/S-042
NDA 21906/S-035

SUPPLEMENT APPROVAL

Abbott Laboratories
Attention: Nancy P. Aiello
Associate Director, Global Pharmaceutical Regulatory Affairs
Dept. PA77/ Bldg. AP34-3
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Aiello:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received November 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kaletra® (lopinavir/ritonavir) Tablets (NDA 21906) and Oral Solution (NDA 21251).

We acknowledge receipt of your amendments dated December 21, 2011 in response to our General Advice letter dated, December 12, 2011.

We also refer to our letter dated October 19, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our October 19, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Kaletra® (lopinavir/ritonavir) Tablets (NDA 21906) and Oral Solution (NDA 21251), consistent with our October 19 and December 12, 2011 letters, as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. The **RECENT MAJOR CHANGES** in the Highlights section of the labeling has been revised as follows:

-------RECENT MAJOR CHANGES-------
Dosage and Administration, Pediatric Patients 2/2011 (2.2)

~~Dosage and Administration, Adult Patients (2.1) 4/2010~~
~~Contraindications, Table 3 (4) 4/2010~~
Warnings and Precautions, Toxicity in Preterm Neonates, 2/2011 (5.2)
Warnings and Precautions, Immune Reconstitution Syndrome, 12/2011 (5.8)
~~Warnings and Precautions (5.1) 6/2010~~
~~Warnings and Precautions (5.4) 4/2010~~

2. The revision date has been changed from 03/2011 to 12/2011 throughout the label.

3. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

   Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including KALETRA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

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

4. The Table 9 in the **7.3 Established and Other Potentially Significant Drug Interactions** section of the package insert has been revised as follows:

Table 9. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
	Other Agents	
HMG-CoA Reductase Inhibitors: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Use atorvastatin with caution and at the lowest necessary dose. Titrate rosuvastatin dose carefully and use the lowest necessary dose; do not exceed rosuvastatin 10 mg/day. See (b) (4) ~~Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or cConsider other HMG-CoA reductase inhibitors such as pitavistatin or pravastatin when coadministered with KALETRA [see Clinical Pharmacology (12.3)]. or fluvastatin in combination with KALETRA.~~

5. The **7.4 Drugs with No Observed or Predicted Interactions with KALETRA section has been revised as follows:**

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

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

6. The **USE IN SPECIFIC POPULATIONS/Pediatric Use** subsection has been revised as follows:

   An open-label, multi-center, dose-finding trial was performed to evaluate the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20mg/mL at a dose of with 300/75 mg/m2 twice

daily plus two NRTIs in HIV-infected infants ≥14 days and < 6 months of age. Results revealed that infants younger than 6 months of age generally had lower lopinavir AUC12 than older children (6 months to 12 years of age), however, despite the lower lopinavir drug exposure observed, antiviral activity was demonstrated as reflected in the proportion of subjects who achieved HIV-1 RNA <400 copies/mL at Week 24 *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.4)]*.

7. The Table 10 and 11 in the **12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics** subsection has been revised as follows:

Table 10. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug for Recommended Alterations in Dose or Regimen

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (in combination with Co-administered drug-/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Efavirenz[1, 2]	600 at bedtime, 9 d	400/100 capsule twice daily, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 at bedtime, 9 d	500/125 tablet twice daily, 10 d	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 at bedtime, 9 d	600/150 tablet twice daily, 10 d	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Fosamprenavir[3]	700 twice daily plus ritonavir 100 twice daily, 14 d	400/100 capsule twice daily, 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Nevirapine	200 twice daily, steady-state (> 1 yr)[4#]	400/100 capsule twice daily, steady-state	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg once daily, 2 wk; twice daily 1 wk[5]	(> 1 yr) 300/75 mg/m^2 twice daily, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Pitavastatin[6]	4 mg once daily, 5 d	400/100 tablet twice daily, 16 d	23	0.93 (0.88-0.98)	0.91 (0.86-0.97)	NA

Pravastatin	20 once daily, 4 d	400/100 capsule twice daily, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifampin	600 once daily, 10 d	400/100 twice daily, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 once daily, 14 d	800/200 twice daily, 9 d[5-7]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 once daily, 14 d	400/400 twice daily, 9 d[6-8]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
					Co-administration of KALETRA and rifampin is not recommended. [See Contraindications (4)]	
Ritonavir[4-3]	100 twice daily, 3-4 wk[#]	400/100 capsule twice daily 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir[7-9]	300 mg once daily, 14 d	400/100 capsule twice daily, 14 d	24	NC[†]	NC[†]	NC[†]
Tipranavir/ritonavir[4-3]	500/200 mg twice daily (28 doses)[#]	400/100 capsule twice daily (27 doses)	21 69	0.53 (0.40, 0.69)[8-10]	0.45 (0.32, 0.63)[8-10]	0.30 (0.17, 0.51)[8-10] 0.48 (0.40, 0.58)[9-11]

All interaction studies conducted in healthy, HIV-1 negative subjects unless otherwise indicated.
1 The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.
2 Reference for comparison is lopinavir/ritonavir 400/100 mg twice daily without efavirenz.
~~2~~3 Data extracted from the fosamprenavir package insert.
~~3~~4 Study conducted in HIV-1 positive adult subjects.
~~4~~5 Study conducted in HIV-1 positive pediatric subjects ranging in age from 6 months to 12 years.
6 Data extracted from the pitavastatin package insert and results presented at the 2011 International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (Morgan, et al, poster #MOPE170)
~~5~~7 Titrated to 800/200 twice daily as 533/133 twice daily x 1 d, 667/167 twice daily x 1 d, then 800/200 twice daily x 7 d, compared to 400/100 twice daily x 10 days alone.
~~6~~8 Titrated to 400/400 twice daily as 400/200 twice daily x 1 d, 400/300 twice daily x 1 d, then 400/400 twice daily x 7 d, compared to 400/100 twice daily x 10 days alone.
~~7~~9 Data extracted from the tenofovir package insert.
~~8~~10 Intensive PK analysis.
~~9~~11 Drug levels obtained at 8-16 hrs post-dose.
~~10 Reference for comparison is lopinavir/ritonavir 400/100 mg twice daily without efavirenz.~~
* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.
† NC = No change.
# For the nevirapine 200 mg twice daily study, ritonavir, and tipranavir/ritonavir studies, KALETRA was administered with or without food. For all other studies, KALETRA was administered with food.

Table 11. Drug Interactions: Pharmacokinetic Parameters for co-administered Drug in the Presence of KALETRA for Recommended Alterations in Dose or Regimen

Co-administered Drug	**Dose of Co-administered Drug (mg)**	**Dose of KALETRA (mg)**		**Ratio (in combination with KALETRA/alone) of co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00**		
			n	**C_{max}**	**AUC**	**C_{min}**
Pitavastatin[4]	4 mg once daily, 5 d	400/100 tablet twice daily, 16 d	23	0.96 (0.84-1.10)	0.80 (0.73-0.87)	N/A
Rifabutin + 25-*O*-desacetyl rifabutin[45]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Rosuvastatin[56]	20 mg once daily, 7 d	400/100 tablet twice daily, 7 d	15	4.66 (3.4, 6.4)	2.08 (1.66, 2.6)	1.04 (0.9, 1.2)
Tenofovir[67]	300 mg once daily, 14 d	400/100 capsule twice daily, 14 d	24	NC[†]	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

All interaction studies conducted in healthy, HIV-1 negative subjects unless otherwise indicated.
1 Ratio of parameters for amprenavir, indinavir, and nelfinavir, are not normalized for dose.
2 Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.

3 Data extracted from the fosamprenavir package insert.
4 Data extracted from the pitavastatin package insert and results presented at the 2011 International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (Morgan, et al, poster #MOPE170).
45 Effect on the dose-normalized sum of rifabutin parent and 25-*O*-desacetyl rifabutin active metabolite.
56 ~~Data extracted from the rosuvastatin package insert and results presented at the 2007 Conference on Retroviruses and Opportunistic Infection (*Hoody, et al, abstract L-107, poster #564*).~~ Kiser, et al. J Acquir Immune Defic Syndr. 2008 Apr 15;47(5):570-8.
67 Data extracted from the tenofovir package insert.
* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.
N/A = Not available.
† NC = No change.

8. The last paragraph of the **PATIENT COUNSELING INFORMATION**/General Information sub-section has been revised as follows:

~~KALETRA is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 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-1 to others through sexual contact, sharing needles, or being exposed to their blood. For their health and the health of others, it is important that they always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. They should also be advised to never re-use or share needles.~~ KALETRA is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using KALETRA.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if KALETRA can be passed to ~~your~~ the baby ~~in~~ through ~~your~~ breast milk and whether it could harm ~~your~~ the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

9. **Medication Guide**:

a. The first paragraph o f the "**What is KALETRA?**" section has been revised as follows:

KALETRA is a prescription anti-human immunodeficiency virus (HIV) ~~HIV~~ medicine that contains two medicines: lopinavir and ritonavir. KALETRA is called a protease inhibitor that is used with other anti-HIV-1 medicines to treat people with ~~human immunodeficiency virus (~~HIV-1~~)~~ infection. HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

b. The eighth bulleted paragraph in the "**What should I tell my doctor before taking KALETRA?/Kaletra may not be right for you. Tell your doctor about all your medical conditions, including if you:**" section should be revised as follows:

- are breast-feeding. ~~Do not breast-feed if you are taking KALETRA. You should not breast-feed if you have HIV-1. If you are a woman who has or will have a baby while taking KALETRA, talk with your doctor about the best way to feed your baby. If your baby does not already have HIV-1, there is a chance that HIV-1 can be passed to your baby through your breast milk.~~ **Do not breastfeed.** We do not know if KALETRA can be passed to ~~your~~ the baby ~~in~~ through your breast milk and whether it could harm ~~your~~ the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

c. The following paragraph has been deleted from the end of the "**If you are not sure if you are taking a medicine above, ask your doctor. How should I take KALETRA?"** section:

~~Avoid doing things that can spread HIV infection. KALETRA does not stop you from passing HIV infection to others. Do not share needles, other injection equipment or personal items that can have blood or body fluids on them, like toothbrushes and razor blades. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.~~

d. HIV was revised to HIV-1 throughout the PI and Medication Guide.

e. The **General information about KALETRA** section has been revised as follows:

~~KALETRA does not cure HIV-1 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-1 infection. Some of these ~~conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.~~ KALETRA does not cure HIV infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using KALETRA.

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration

Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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 Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

KENDALL A MARCUS
02/17/2012