



NDA 21226/S-035

SUPPLEMENT APPROVAL

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

Dear Ms. Aiello:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kaletra[®] (lopinavir/ritonavir) Capsules, 133.3mg/33.3mg.

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.

This supplemental new drug application provides for revisions to the labeling for Kaletra[®] (lopinavir/ritonavir) Capsules, 133.3mg/33.3mg, consistent with our October 19 and December 12, 2011 letters, as follows (additions are noted by underline and deletions are noted by ~~striketrough~~).

1. The Table 3 and 4 in the **CLINICAL PHARMACOLOGY/Drug-drug Interactions** subsection of the package insert has been revised as follows:

<p>Table 3. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug (See PRECAUTIONS – Table 11 for Recommended Alterations in Dose or Regimen)</p>
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Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (in combination with Co-administered drug-/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C _{max}	AUC	C _{min}
Amprenavir	750 BID, 10 d	400/100 BID, 21 d	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.90 (0.78, 1.06)	0.90 (0.79, 1.02)	0.92 (0.78, 1.10)
Efavirenz ¹	600 QHS, 9 d	400/100 BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
Fosamprenavir ²	700 BID plus ritonavir 100 BID, 14 d	400/100 BID, 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 BID, 10 d	400/100 BID, 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 BID, steady-state (> 1 yr) ³	400/100 BID, steady-state	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID 1 wk ⁴	(> 1 yr) 300/75 mg/m ² BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Omeprazole	40 QD, 5 d	400/100 tablet BID, 10 d	12	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)
	40 QD, 5 d	800/200 tablet QD, 10 d	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
<u>Pitavastatin⁵</u>	<u>4 mg QD, 5 d</u>	<u>400/100 tablet BID, 16 d</u>	<u>23</u>	<u>0.93 (0.88-0.98)</u>	<u>0.91 (0.86-0.97)</u>	<u>NA</u>
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 QD, 10 d	400/100 BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)

Ranitidine	150 single dose	400/100 tablet BID, 10 d	12	0.99 (0.95, 1.03)	0.97 (0.93, 1.01)	0.90 (0.85, 0.95)
	150 single dose	800/200 tablet QD, 10 d	10	0.97 (0.95, 1.00)	0.95 (0.91, 0.99)	0.82 (0.74, 0.91)
Rifampin	600 QD, 10 d	400/100 BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 QD, 14 d	800/200 BID, 9 d ⁵⁶	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 QD, 14 d	400/400 BID, 9 d ⁶⁷	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
					Co-administration of KALETRA and rifampin is not recommended. (See PRECAUTIONS – Table 10 and Table 11)	
Ritonavir ³	100 BID, 3-4 wk	400/100 BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir ⁷⁸	300 mg QD, 14 d	400/100 BID, 14 d	24	NC [†]	NC [†]	NC [†]
Tipranavir/ritonavir ³	500/200 mg BID (28 doses)	400/100 capsule BID (27 doses)	21 69	0.53 (0.40, 0.69) ⁸²	0.45 (0.32, 0.63) ⁸²	0.30 (0.17, 0.51) ⁸² 0.48 (0.40, 0.58) ⁹¹⁰
<p>All interaction studies conducted in healthy, HIV-negative subjects unless otherwise indicated.</p> <p>1 The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.</p> <p>2 Data extracted from the fosamprenavir package insert.</p> <p>3 Study conducted in HIV-positive adult subjects.</p> <p>4 Study conducted in HIV-positive pediatric subjects ranging in age from 6 months to 12 years.</p> <p>5 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)</p> <p>⁶⁵ Titrated to 800/200 BID as 533/133 BID x 1 d, 667/167 BID x 1 d, then 800/200 BID x 7 d, compared to 400/100 BID x 10 days alone.</p> <p>⁷⁶ Titrated to 400/400 BID as 400/200 BID x 1 d, 400/300 BID x 1 d, then 400/400 BID x 7 d, compared to 400/100 BID x 10 days alone.</p> <p>⁸⁷ Data extracted from the tenofovir package insert.</p> <p>⁹⁸ Intensive PK analysis.</p> <p>¹⁰⁹ Drug levels obtained at 8-16 hrs post-dose.</p> <p>* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.</p> <p>N/A = Not available.</p> <p>† NC = No change.</p>						

Table 4. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of KALETRA (See PRECAUTIONS – Table 11 for Recommended Alterations in Dose or Regimen)						
Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)	n	Ratio (in combination with KALETRA/alone) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Amprenavir ¹	750 BID, 10 d combo vs. 1200 BID, 14 d alone	400/100 BID, 21 d	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Atorvastatin	20 QD, 4 d	400/100 BID, 14 d	12	4.67 (3.35, 6.51)	5.88 (4.69, 7.37)	2.28 (1.91, 2.71)
Desipramine ²	100 single dose	400/100 BID, 10 d	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	N/A
Efavirenz	600 QHS, 9 d	400/100 BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum [®])	400/100 BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Fosamprenavir ³	700 BID plus ritonavir 100 BID, 14 d	400/100 BID, 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir ¹	600 BID, 10 d combo nonfasting vs. 800 TID, 5 d alone fasting	400/100 BID, 15 d	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A

Nelfinavir ¹	1000 BID, 10 d combo vs. 1250 BID, 14 d alone	400/100 BID, 21 d	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)
M8 metabolite				2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)
Nevirapine	200 QD, 14 d; BID, 6 d	400/100 BID, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho Novum [®])	400/100 BID, 14 d	12	0.84 (0.75, 0.94)	0.83 (0.73, 0.94)	0.68 (0.54, 0.85)
Pitavastatin ⁴	4 mg QD, 5 d	400/100 tablet BID, 16 d	23	0.96 (0.84-1.10)	0.80 (0.73-0.87)	N/A
Pravastatin	20 QD, 4 d	400/100 BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	150 QD, 10 d; combo vs. 300 QD, 10 d; alone	400/100 BID, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-O- desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25-O- desacetyl rifabutin ⁴⁵				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Rosuvastatin ⁵⁶	20 mg QD, 7 d	400/100 tablet BID, 7 d	15	4.66 (3.4, 6.4)	2.08 (1.66, 2.6)	1.04 (0.9, 1.2)
Saquinavir ¹	800 BID, 10 d combo vs. 1200 TID, 5 d alone,	400/100 BID, 15 d	14	6.34 (5.32, 7.55)	9.62 (8.05, 11.49)	16.74 (13.73, 20.42)
	1200 BID, 5 d combo vs. 1200 TID, 5 d alone	400/100 BID, 20 d	10	6.44 (5.59, 7.41)	9.91 (8.28, 11.86)	16.54 (10.91, 25.08)
Tenofovir ⁶⁷	300 mg QD, 14 d	400/100 BID, 14 d	24	NC [†]	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

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

1 Ratio of parameters for amprenavir, indinavir, nelfinavir, and saquinavir are not normalized for dose.

2 Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.

3 Data extracted from the fosamprenavir package insert.

4 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).

54 Effect on the dose-normalized sum of rifabutin parent and 25-O-desacetyl rifabutin active metabolite.

65 ~~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.

76 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.

2. In the “Warnings - Drug Interactions” section, the paragraph on concomitant use of KALETRA and statins has been revised as follows:

Concomitant use of lovastatin or simvastatin is contraindicated. 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 Precautions – Other Drugs and Tables 3 and 4 for drug interaction data with other HMG-CoA reductase inhibitors.

(b) (4)

~~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.~~

3. The **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 carinii 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. A paragraph begins with "Patients should be informed that KALETRA is not a cure for HIV....." in the **PRECAUTIONS/Information for Patients** sub-section has been revised as follows:

~~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 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.

5. The **PRECAUTIONS/Drug Interactions** sub-section has been revised as follows:

Table 11. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction See CLINICAL PHARMACOLOGY for Magnitude of Interaction – Table 3 and Table 4

[illegible]

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

6. **PRECAUTIONS/Other Drugs** sub-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.

7. **Patient Information Labeling:**

- a. The “**Does KALETRA cure HIV or AIDS?**” section has been revised as follows:
~~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.~~ 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.

- b. The “**Does KALETRA reduce the risk of passing HIV to others?**” section has been deleted.

~~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.~~

- c. In the **Patient Information Labeling** section, under “**Medicines You Should Not Take with KALETRA**,” the statement on statins has been revised to read as follows:
~~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.~~ Do not take KALETRA with the cholesterol-lowering medicines Mevacor® (lovastatin) or Zocor® (simvastatin) because of possible serious reactions.
- d. Under the subsection, “**Medicines that require dosage adjustment**”, the following

statement has been added at the end of this section: If you are taking the cholesterol lowering medicines Lipitor® (atorvastatin) or Crestor® (rosuvastatin), your doctor may need to lower your dose of Lipitor or Crestor while you are taking KALETRA.

- e. The second bulleted paragraph in the “**What should I tell my doctor before taking KALETRA?**” section has been revised as follows: 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. 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.
8. The revision date has been changed from 04/2010 to 12/2011 at the end of the label.

We have completed our review of this supplemental application, as amended. It is 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