DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-906/S-015
NDA 21-251/S-024

Abbott Laboratories
Attention: Mary S. Konkowski
Manager, Global Pharmaceutical Regulatory Affairs
Dept. PA76 / BLDG. AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Konkowski:

Please refer to your supplemental new drug applications dated April 4, 2008, received April 4, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KALETRA®, (lopinavir/ritonavir) Tablets and Oral Solution.

Reference is made to our correspondence dated September 5, and October 2, 2008. We acknowledge receipt of your submissions dated May 15, August 8 and September 26, 2008. Reference is also made to the telephone conversations and electronic mail correspondence dated October 2 and October 3, 2008.

These supplemental new drug applications provide for the following revisions to the package insert:

- Table 9 in the Drug Interactions Section (Section 7) is being updated with information on drug interactions between KALETRA® and bupropion, efavirenz, maraviroc, phenytoin, vincristine, vinblastine and voriconazole.
- Tables 10 and 11 in the Clinical Pharmacology Section (Section 12.3) are being revised to remove the KALETRA®-Atorvastatin drug interaction study (M99-057) information as recommended by FDA in the December 18, 2007, letter to Abbott regarding MDS Pharma.
- Table 10 in the Clinical Pharmacology section is also being updated to add the efavirenz data from study M10-066.

We have 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 and with the minor editorial revisions agreed to on October 2 and October 3, 2008, as listed below. Reference is made to your approved request dated October 2, 2008, to defer making the labeling change in recommendation #6 until the appropriate research has been done to determine which clinical studies were conducted under fed conditions.

Kaletra additional changes to section 7.3 (Established and Other Potentially Significant Drug Interactions), Table 9

1) Bupropion

Antidepressant: bupropion	↓ bupropion ↓ active metabolite, hydroxybupropion	Concurrent administration of bupropion with KALETRA may decrease plasma levels of both bupropion and its active metabolite (hydroxybupropion). Patients receiving KALETRA and bupropion concurrently should be monitored for an adequate clinical response to bupropion.

2) Efavirenz

Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ lopinavir	KALETRA dose increase is recommended in all patients *[See DOSAGE AND ADMINISTRATION (2.1) and CLINICAL PHARMACOLOGY (12.3)]*. Increasing the dose of KALETRA tablets to 500/125 mg (given as two 200/50 mg tablets and one 100/25 mg tablet) twice daily co-administered with efavirenz resulted in similar lopinavir concentrations compared to KALETRA tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz. Increasing the dose of KALETRA tablets to 600/150 mg (given as three 200/50 mg tablets) twice-daily co-administered with efavirenz resulted in significantly higher lopinavir plasma concentrations compared to KALETRA tablets 400/100 mg twice-daily without efavirenz. KALETRA should not be administered once-daily in combination with efavirenz or nevirapine. *[See DOSAGE AND ADMINISTRATION (2.1) and CLINICAL PHARMACOLOGY (12.3)]*.

3) Phenytoin

Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ lopinavir ↓ phenytoin	KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly and should be used with caution. KALETRA should not be administered once-daily in combination with carbamazepine, phenobarbital, or phenytoin. In addition, co-administration of phenytoin and KALETRA may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with KALETRA.

4) Vincristine and Vinblastine

Anticancer Agents: vincristine, vinblastine	↑anticancer agents	Concentrations of vincristine or vinblastine may be increased when co-administered with lopinavir/ritonavir (KALETRA) resulting in the potential for increased adverse events usually associated with these anticancer agents Consideration should be given to temporarily withholding the ritonavir-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when lopinavir/ritonavir (KALETRA) is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.

5) HMG-CoA Reductase Inhibitors:

(PLEASE DELETE THE ASTERISK IN THE TABLE BELOW)

HMG-CoA Reductase Inhibitors: atorvastatin***** rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.

6) Update the Table 10 footnotes to indicate which of the listed Table 10 studies were conducted under fed conditions.

7) In regards to the requested changes to Table 10, please shift the "…with efavirenz 600mg QHS compared to 400 mg dose BID alone" information to a footnote as indicated below since it applies to all the lopinavir/ritonavir-efavirenz drug-drug interaction studies.

Efavirenz[1, 10]	600 QHS, 9 d	400/100 capsule BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 QHS, 9 d	500/125 tablet BID, 10 d	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 QHS, 9 d	600/150 tablet BID, 10 d	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)

10-Reference for comparison is lopinavir/ritonavir 400/100 mg BID without efavirenz

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

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to, except for including the revisions listed, the enclosed labeling (text for the package insert and text for the patient package insert,) and/or submitted labeling (package insert and patient package insert submitted September 26, 2008). These revisions are terms of the NDA supplement approval. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission **"SPL for approved supplements NDA 21-906/S-015 and NDA 21-251/S-024."**

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
Food and Drug Administration
Suite 12B05
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 Kwadwo (Kojo) Awuah, Pharm.D., Regulatory Project Manager, at (301) 796-0608.

Sincerely,

{See appended electronic signature page}

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

Enclosures: Package Insert (PI)
Patient Package Insert (PPI)

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
10/3/2008 03:42:04 PM
NDA 21-251, 21-906