DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-226/S-003
NDA 21-251/S-004

Abbott Laboratories
Attention: Rebecca A. Welch
Associate Director, PPD Regulatory Affairs
D-491/AP6B-1SW
100 Abbott Park Road
Abbott Park, IL 60064-6108

Dear Ms Welch:

Please refer to your supplemental new drug applications dated March 19, 2001, April 12, 2001, and July 12, 2001, received March 20, 2001, April 13, 2001, and July 13, 2001 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 amended submissions dated:

May 16, 2001	December 03, 2001
August 27, 2001	December 11, 2001
August 30, 2001	January 09, 2002
October 16, 2001	January 10, 2002
November 06, 2001	January 14, 2002
November 21, 2001	January 16, 2002

These supplemental new drug applications contained 48-week safety and efficacy data (updated from 24-week data) from three studies 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 a controlled study 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.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

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

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 & 21-251/S-003" and "FPL for approved supplement NDA 21-251 & 21-226/S-004." Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your post-marketing study commitments in your amended submission dated January 16, 2002. These commitments are listed below.

1. Evaluate the relative treatment response, safety and tolerability of Caucasians vs. Blacks using data from study 888 and the entire clinical trial data available to Abbott. Analyses may be submitted during review of Study M98-888 clinical study report (CSR) for Traditional Approval, projected for submission the first quarter 2002.

   The sponsor commits to providing the treatment response, safety and tolerability, of Caucasians vs. Blacks using data from study 888 and the entire clinical trial data available to Abbott by 2nd Q '02.

2. Evaluate the use of Kaletra in a population of more extensively treated pediatric patients, with special attention to identifying whether the currently approved dosing recommendation are adequate for children who have failed treatment with multiple ($\geq$2) other PIs.

   The sponsor commits to support a pediatric study which will look at patients who have been previously treated. An example of the proposed study design is PACTG study P1038 which currently plans to enroll 32 patients between the ages of 2 to 18 years to achieve an IQ >15 in pediatric patients previously treated with PIs. Data from this study will be submitted by July 2004.

We also remind you of your outstanding post-marketing study commitments outlined in the original accelerated approval letter dated September 15, 2000.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to these NDAs. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27) in infants <6 months of age and adolescents 12-16 years of age. We are deferring submission of your pediatric studies in these age groups until July, 2004. However, in the interim, please submit your pediatric drug development plans for these age groups within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

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. We remind you that a formal Written Request was issued to you on March 31, 1999 and amended June 18, 2001. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, 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 the requirements for an approved NDA set forth under 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