NDA 21-226
NDA 21-251

Abbott Laboratories
Attention: Rebecca A. Welch
Associate Director, PPD Regulatory Director
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 66064-6108

Dear Ms. Welch:

Please refer to your new drug applications (NDA) both dated May 31, 2000, received June 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for KALETRA (400 mg lopinavir/100 mg ritonavir) oral capsules and KALETRA (80mg lopinavir/20mg ritonavir) oral solution.

The User Fee goal date for these applications is December 1, 2000.

We acknowledge receipt of your submissions dated:

December 28, 1999	June 21, 2000	September 7, 2000
January 12, 2000	June 28, 2000	September 13, 2000
March 31, 2000	July 7, 2000	September 14, 2000
April 10, 2000	July 27, 2000 (2)	September 15, 2000 (3)
May 17, 2000	August 2, 2000	
May 31, 2000	August 7, 2000	
June 7, 2000	August 16, 2000	
June 9, 2000	August 30, 2000	

These new drug applications provide for the use of KALETRA in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age six months and older.

We have completed the review of these applications, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve KALETRA for use as recommended in the agreed upon draft label dated September 15, 2000. Accordingly, these applications are approved under 21 CFR 314 subpart H. Approval is effective on the date of this letter. Marketing of these drug products and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted September 15, 2000, patient package insert submitted September 15, 2000, immediate container and carton labels submitted September 15, 2000). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please 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. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, these submission should be designated **"FINAL PRINTED LABELING"** for approved NDA 21-226 and 21-251. Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing studies (Subpart H) as specified in your submission dated September 15, 2000**,** in which you agreed to submit the results from the final study analyses of the following two ongoing phase 3 studies of the safety and efficacy of KALETRA to support traditional approval: Study M98-863, "A Randomized, Double-Blind, Phase III Study of ABT-378/Ritonavir Plus Stavudine and Lamivudine vs. Nelfinavir Plus Stavudine and Lamivudine in Antiretroviral-Naïve HIV-Infected Subjects" and Study M98-888, "A Randomized, Open-Label, Phase III Study of ABT-378/ritonavir in Combination with Nevirapine and Two Nucleoside Reverse Transcriptase Inhibitors vs Investigator Selected Protease Inhibitor(s) in Combination with Nevirapine and Two NRTIs in Antiretroviral-Experienced HIV-Infected Subjects".

Final study reports should be submitted to these NDAs as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Subpart H".

In addition, we note your following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments, along with any completion dates agreed upon, include:

Phase 4 Commitments:

Chemistry

1. A commitment to reassess the drug substance specification and the drug product specification when stability studies on the first three commercial scale lots of the capsules have been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed specifications, through a prior approval supplement to NDA 21-226.

Projected Submission date: First quarter 2003.

2. A commitment to reassess the drug product specification when stability studies on the first three commercial scale lots of the oral solution have been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed specifications, through a prior approval supplement to NDA 21-251.

   Projected Submission date: First quarter 2003.

Microbiology

3. Analyze isolates from patients with virologic failure on KALETRA to determine associations between protease mutations and *in vitro* shifts in susceptibility to define the resistance profile of lopinavir.

   Projected Submission Date: Based on the availability of isolates, by fourth quarter 2001; data would be provided by second quarter 2002.

4. Continue genotypic and phenotypic analysis of isolates from patients in ongoing Studies M97-765 and M98-957 who experience loss of virologic response.

   Projected Submission Date: Second quarter 2001.

5. Assess the genotypic basis of drug susceptibility attributable to extragenic sites, such as the protease cleavage sites.

   Projected Submission Date: Second quarter 2001.

6. Conduct *in vitro* combination activity studies.

   Projected Submission Date: Third quarter 2001.

7. Evaluate the cross-resistance potential between KALETRA and amprenavir.

   Projected Submission Date: Based on the availability of isolates, by fourth quarter 2001; data would be completed by second quarter 2002.

Pharmacology/toxicology

8. Continue carcinogenicity studies and submit final reports.

   Projected Submission Date: Fourth quarter 2001.

Clinical Pharmacology

9. Evaluate KALETRA pharmacokinetics in subjects with mild and moderate hepatic impairment, to allow the determination of dosing recommendations, through the conduct of a pharmacokinetic study.

   Projected Submission Date: Third quarter 2002.

10. Establish appropriate dosing recommendations for the coadministration of KALETRA with other approved protease inhibitors through the conduct of drug interaction studies.

    Projected Submission Date: Third quarter 2002.

11. Determine, *in vivo*, the extent to which KALETRA inhibits CYP2D6. Consideration will be given to conducting a drug interaction study with KALETRA and desipramine.

    Projected Submission Date: First quarter 2002.

12. Further evaluation of the pharmacokinetics of KALETRA and nevirapine in HIV-infected adults from Study M97-765

    Projected Submission Date: First quarter 2002.

13. Explore dosing recommendations for coadministration of KALETRA and rifampin, with additional ritonavir.

    Projected Submission Date: Third quarter 2002.

14. Explore dosing recommendations for the coadministration of KALETRA plus approved protease inhibitor(s) plus efavirenz/nevirapine through analysis of data from the Expanded Access Program.

    Projected Submission Date: Third quarter 2001.

15. Evaluate pharmacokinetic/pharmacodynamic relationships in Studies M98-957 and M99-049.

Projected Submission Date: Data for M98-957 by second quarter 2001; based on enrollment projection, 48 week data from M99-049 should be available third quarter 2002.

Clinical

16. Continue to investigate the efficacy of once daily administration of KALETRA through the conduct of Study M99-056.

    Projected Submission Date: Fourth quarter 2001.

17. Continue to evaluate the activity of higher doses of KALETRA in patients exhibiting virologic failure or showing reduced susceptibility to multiple protease inhibitors through the conduct of Study M99-049.

    Projected Submission Date: Based on enrollment projection, the 48 week report should be available third quarter 2002.

18. Development of educational materials for patients and healthcare workers regarding avoidance of drug interactions.

    Projected Submission Date: Ongoing commitment to provide this information.

19. Continued evaluation of suspected protease inhibitor class adverse events including (a) establishment of an intercompany collaboration, or company based registry to collect data on patients who develop fractures or avascular hip necrosis while receiving antiretroviral therapy and (b) fat redistribution. This will include investigation of mechanisms for development of fat redistribution in patients receiving protease inhibitors, the incidence of this event, and the potential for long-term consequences. In addition, ongoing and future clinical trials should provide appropriate monitoring for these events and for any lipid-related disorders.

    Projected Submission Date: Ongoing commitment with update provided no later than third quarter 2002.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to these NDAs. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to these NDAs as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to these NDAs. The status summary should include the number of patients entered in each study,

expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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) for pediatric patients under the age of 6 months. Accordingly, we are deferring submission of your studies in pediatric patients under the age of 6 months until June 1, 2003.

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). Please refer to the Pediatric Written Request dated March 31, 1999. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please submit one market package of the drug product when it is available.

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 Sylvia D. Lynche, PharmD, Regulatory Management Officer, at (301) 827-2335.

Sincerely,

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research