

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-226**

**21-251**

**CORRESPONDENCE**

HFD-530/SLynche

NDA 21-226  
NDA 21-251

JUN 9 2000

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

Dear Ms. Welch:

We have received your new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Products: Lopinavir/Ritonavir 133.3 mg/33.3 mg capsules and  
Lopinavir Ritonavir 80 mg/20 mg oral solution.

Therapeutic Classification: Priority (P)

Date of Application: May 31, 2000

Date of Receipt: June 1, 2000

Our Reference Number: NDA 21-226 and NDA 21-251

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 1, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 1, 2000.

We have determined that this application will be reviewed under 21 CFR 314 Subpart H (accelerated approval). We remind you that as required under 21 CFR 314.550, unless otherwise informed by the Agency, you must submit for Agency review before approval of this application copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days after marketing approval.

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), and therefore we are deferring submission of your pediatric studies until July 1, 2001.

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 make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. 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). 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 cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Antiviral Drug Products, HFD-530  
Attention: Division Document Room  
NUMBER  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Antiviral Drug Products, HFD-530  
Attention: Division Document Room  
NUMBER  
9201 Corporate Blvd.  
Rockville, Maryland 20850-3202

NDA 21-226

Page 3

If you have any questions, call Sylvia Lynche, Pharm.D., Regulatory Management Officer, at (301) 827-2335.

Sincerely,

/S/

Anthony W/DeCicco, R.Ph.  
Chief, Project Management Staff  
Division of Antiviral Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-226 and NDA 21-251

HFD-530/Div. Files

HFD-530/PM/S.Lynche

HFD-530/RRO/Struble

HFD-530/MOTL/Murray

HFD-530/MTL/Iacono-Connors

HFD-530/MR/O'Rear

HFD-530/PTTL/Farrelly

HFD-530/PTR/ZhangH

HFD-530/BPTL/Reynolds

HFD-530/BPR/Rajagopalan

HFD-530/SR/Soon

HFD-530/STL/Aras

HFD-530/CTL/Miller

HFD-530/CR/LoK

HFD-530/MR/Lewis

DISTRICT OFFICE

ACKNOWLEDGEMENT (AC)



**ABBOTT**

**Pharmaceutical Products Division**

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Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

March 31, 2000

Mellon Bank  
Three Mellon Bank Center  
27th Floor (FDA 360909)  
Pittsburgh, PA 15259-0001

**Subject: USER FEE LD. NUMBER 3928**

Dear Sir or Madam:

Enclosed is a check in the amount of \$285,740 to cover the user fee payment for the following application:

Generic Name:	ABT-378
Indication for Use:	Treatment of HIV Infection
Type of Submission:	New Drug Application
NDA Number:	NO21251
Name of Sponsor:	Abbott Laboratories
Address:	D-491, Building AP6B-1SW PPD Regulatory Affairs 100 Abbott Park Road Abbott Park, Illinois 60064-6108
Contact Person:	Peter Noblin
Telephone Number:	(847) 937-5091

We would appreciate receiving a receipt for this payment; for your convenience, I have enclosed a self-addressed, stamped envelope.

Sincerely,

Peter Noblin  
Associate Director, Regulatory Affairs

Enclosures: Abbott Check Number D01393850, User Fee Cover Sheet,  
Self-Addressed, Stamped Envelope

cc: Rebecca Welch, D-491, AP6B-1  
Paula Bourland, D-404, AP9A-1  
Sandra Harder, D-387, AP6C-1  
Kathy Christianson, D-344, AP6D-1

HPD-550/Lynche

Abbott Laboratories  
Attention: Rebecca Welsh  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

MAR 31 1999

Dear Ms. Welsh:

Reference is made to your Proposed Pediatric Study Request submitted on March 4, 1999, for ABT-378 to IND         

To obtain needed pediatric information on the drug product ABT-378/ritonavir, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

**Type of studies:**

Multiple-dose pharmacokinetic, safety and activity study of ABT-378/ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients.

Multiple-dose pharmacokinetic and safety study of ABT-378/ritonavir in HIV-exposed neonates (born to HIV-infected mothers).

**Indication to be studied:**

Treatment of HIV infection

**Age group in which studies will be performed:**

HIV-infected pediatric patients from 1 month to 16 years and HIV-exposed neonates (born to HIV-infected mothers).

**Drug Information**

Dosage form: tablets and age appropriate-formulation

Route of administration: oral

Regimen: to be determined by development program

**Drug specific safety concerns:**

Gastrointestinal effects, liver function test abnormalities, metabolic disorders such as hyperglycemia, hyperlipidemia, and abnormal fat redistribution.

**Statistical information, including power of study and statistical assessments:**

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients.

Descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

Studies should include an adequate number of patients to characterize pharmacokinetics over the age range studied, taking into account inter-subject and intra-subject variability. The number of subjects should be uniformly distributed across the age range studied.

**Clinical endpoints including primary efficacy endpoints:**

Pharmacokinetics

Parameters such as  $C_{max}$ ,  $C_{min}$ ,  $T_{max}$ ,  $t_{1/2}$ , AUC

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of six months. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of 6 months from the initiation of therapy. In addition, please submit plans for long-term safety monitoring in HIV-exposed neonates (born to HIV-infected mothers) and HIV-infected pediatric patients who have received ABT-378/ritonavir.

Activity

Assessment of changes in plasma HIV RNA levels and in CD4 cell counts.

**Labeling that may result from the study (ies):**

Information regarding dosing, safety and activity in HIV-infected pediatric population and information regarding dosing and safety in HIV-exposed neonates (born to HIV-infected mothers).

**Format of reports to be submitted:**

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. Please include other information as appropriate.

**Timeframe for submitting reports of the study(ies):**

Reports of the above studies must be submitted to the Agency on or before July 1, 2001. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written

Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*), with FDA before developing pediatric protocols. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA or as a new drug application, as appropriate, with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, contact Sylvia D. Lynche, Pharm.D., Regulatory Project Manager, at 301-827-2335.

Sincerely yours,

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*/S/*  
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M. Dianne Murphy, M.D. *U*  
Director  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Concurrence:

HFD-530/MO Team Leader/Murray /S/3/12/99  
HFD-5530/RRO/Struble 3/12/99  
HFD-530/SCSO/DeCicc /S/3/16/99  
HFD-530/DD/Birnkrant / 3/17/99  
HFD-530/Director/Jolsor /S/3/17/99  
HFD-530/MOTL/Lvrtw /S/3/17/99  
cc: 3-24-99

- Archival IND 55,984
- HFD-530/Division file
- HFD-530/PM/Lynche
- HFD-530/MO Team Leader/Murray
- HFD-5530/RRO/Struble
- HFD-530/Biopharm/Reynolds/Gillespie
- HFD-530/Chem/Miller/Lunn
- HFD-104/Office Director/Dr. Murphy
- HFD-600/Office of Generic Drugs
- HFD-2/MLumpkin
- HFD-104/DMurphy
- HFD-6/Kroberts

**PEDIATRIC WRITTEN REQUEST LETTER  
INFORMATION REQUEST (IR)**

**Abbott Laboratories  
Attention: Rebecca Welch  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-3500**

**Dear Ms Welch:**

**Please refer to your Investigational New Drug Application (IND) submitted pursuant to Section 505 (i) of the Federal Food, Drug, and Cosmetic Act for ABT-378/ritonavir for the treatment of HIV infection.**

**The purpose of this letter is to summarize our comments regarding the proposed development plans for ABT-378/ritonavir as discussed during an end-of-phase 2 meeting on November 4, 1998.**

**During this meeting it was agreed that your dose selection for phase 3 clinical trials and proposed development plan outlined in serial 078, dated October 6, 1998, are reasonable. In addition, on November 4, 1998, we discussed clinical trial design issues in the evaluation of drug efficacy in patients who have demonstrated loss of virologic response after one or more "standard" antiretroviral regimens. We are aware of the difficulties in studying antiviral treatments in this setting and we appreciate your efforts in attempting to develop clinical studies in this patient group. We welcome the opportunity to continue to work with you on this important issue and hope to reach agreement on a clinical trial design that is likely to yield important clinical information.**

**Specific comments for study M98-863 "A Randomized, Open-Label, Phase 3 Study of ABT-378/Ritonavir Plus Stavudine and Lamivudine vs. Nelfinavir Plus Stavudine and Lamivudine in Antiretroviral-Naïve HIV-Infected Subjects," will be sent to you via facsimile. In addition, please consider the following items in your drug development program for ABT-378/ritonavir.**

- 1. The proposed uncontrolled design of study M98-888, "An Open-Label, Single Arm, Phase 3 Study of ABT-378/ritonavir in Treatment of HIV-Infected Patients Who Have Detectable HIV RNA During Protease Inhibitor Therapy," does not permit one to evaluate ABT-378/ritonavir's contribution toward antiviral activity. Therefore, it seems unlikely that the study results would provide additional clinical information meriting inclusion in the Description of Clinical Studies section of a package insert. Please consider conducting a controlled trial in antiretroviral experienced patients as part of your phase 3 development program.**

As stated above, we would appreciate further discussions via teleconference regarding trial design options and analysis plans.

2. Accelerated approval regulations do not diminish the requirement for an adequate safety database. Safety data in at least 500-1000 individuals followed for a minimum of six months should be included in an NDA by the time of the safety update.
3. Due to recent problems with the interpretation of 16-week virologic data, we request that 24 weeks of HIV RNA and CD4 data be included in an NDA for accelerated approval at the time of submission.
4. FDA places a high priority on the inclusion of data from children in an NDA. Please refer to the letter dated November 4, 1998, regarding pediatric exclusivity issues.
5. Please consider conducting drug-interaction studies with methadone and lipid-lowering agents, particularly HMG Co-A reductase inhibitors.
6. Information regarding viral resistance is important in evaluating an antiretroviral agent. We strongly encourage incorporation of resistance sub-studies into each phase 3 trial. Please submit your proposals for each study for further discussion.
7. If you choose to utilize an experimental (unapproved) plasma HIV RNA assay in your phase 3 trials, you are encouraged to provide relevant data as outlined in our facsimile dated November 2, 1998, as soon as possible.
8. Please submit your plans for traditional approval as soon as possible.

Should you have any questions, please contact Sylvia Lynche, Regulatory Management Officer at (301) 827-2335.

Sincerely,

Heidi M. Jolson, M.D., M.P.H.  
Director  
Division of Antiviral Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

**Concurrence:**

HFD-530/Dep. Dir./D.Birnkrant  
HFD-530/A. Dir./W.Dempsey  
HFD-530/MTL/J.Murray  
HFD-530/RRO/K.Struble  
HFD-530/Mirco TL/L.Iacono-Connors  
HFD-725/Stats TL/P.Flyer  
HFD-880/Biopharm TL/K.Reynolds  
HFD-880/Biopharm/B.Gillespie  
HFD-725/Stats TL/P.Flyer  
HFD-530/CPM/A.DeCicco

**Cc:**

Original IND -  
Division File  
HFD-530/MTL/J.Murray  
HFD-530/RRO/K.Struble  
HFD-530/Pharm TL/J.Farrelly  
HFD-590/Pharm/S.Kunder  
HFD-530/Chem TL/S.Miller  
HFD-530/Chem/K.Lo  
HFD-530/Mirco TL/L.Iacono-Connors  
HFD-880/Biopharm TL/K.Reynolds  
HFD-880/Biopharm/B.Gillespie  
HFD-725/Stats TL/P.Flyer  
HFD-725/Stats/T.Hammerstrom  
HFD-530/RMO/S.Lynch

**END OF PHASE 2 LETTER**