CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226/S-003

21-251/S-004

ADMINISTRATIVE DOCUMENTS

Declaration of Patent

The undersigned declares that the following patent covers the compound for ABT-378 .

Patent #	Expiration Date	Topic of Patent
5,914,332	December 13, 2015	Compound

The sponsor, Abbott Laboratories, certifies that no previous patents claim this drug formulation.

Rebecca A. Welch
Associate Director
PPD Regulatory Affairs
Abbott Laboratories

Certification Requirement
For Approval of a Drug Product
Concerning Using Services of Debarred Persons

- DEBARMENT STATEMENT -

Any application for approval of a new drug product submitted on or after June 1, 1992, per FD&C Act Section 306 (k)(1), must include:

> (1) a certification that the applicant did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with such application.

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with such application.

[Generic Drug Enforcement Act of 1992, Section 306(k)(1) of 21 USC 335a(k)(1)].

Rebecca A. Welch

3/31/00

Rebecca A. Welch
Associate Director, PPD Regulatory Affairs
Abbott Laboratories
Dept. 491, Bldg. AP6B-1
(847) 937-8971
100 Abbott Park Road
Abbott Park, Illinois 60064-6108

Reference is made to New Drug Application 21-226, ABT-378 (lopinavir) Capsules. At this time we wish to include in this application the following patent information as allowed per CFR 314.53(a). The sponsor, Abbott Laboratories, certifies that no previous patents claim this compound.

United States Patent No. 5,914,332 was issued on June 22, 1999. This patent claims the compound.

Patent #	5,914,332
Name of Patent Owner	Abbott Laboratories
Type of Patent	Compound
Expiration Date	December 13, 2015

A Patent Declaration is attached. A copy of this information will also be sent to the FDA Drug Information Services.

As provided by 21 CFR 314.53(e), the sponsor is requesting this patent information be published in the next supplement to the Orange Book list. In addition, we understand that this patent information will be placed on public display in the FDA Freedom of Information Staff Office.

EXCLUSIVITY SUMMARY for NDA # 21-226 & 21-251 SUPPL # 003 & 004

Trade Name Kaletra® **Generic Name lopinavir/ritonavir**

Applicant Name Abbott Laboratories **HFD- 530**

Approval Date January 18, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /**X**/

   b) Is it an effectiveness supplement? YES /**X**/ NO /___/

      If yes, what type(SE1, SE2, etc.)? **SE-8**

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /**X**/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /__X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /__X__/ NO /___/

If yes, NDA # **21-226 & 21-251** Drug Name **Kaletra Capsules & Kaletra Oral Solution**

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

Sean J. Belouin, R.Ph
Regulatory Project Manaager
Division of Antiviral Drug Products

January 15,2002
Date

/S/

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products

January 18,2002
Date

cc:
Archival NDA 21-226/S-003 & NDA 21-251/S-004
HFD-530/Division File
HFD-530/RPM/Belouin
HFD-530/CRPM/DeCicco
HFD-530/DivDir/Birnkrant
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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
1/18/02 03:07:45 PM

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

NDA Number:	021226	**Trade Name:**	KALETRA
Supplement Number:	003	**Generic Name:**	LOPINAVIR; RITONAVIR
Supplement Type:	SE8	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF HIV INFECTION
Original NDA Action Date:	3/20/01		

Indication # 1 Treatment of HIV infection

Comments (if any): 1/18/02 - This supplement was reviewed simultaneously with NDA 21-251, SE8/004, for Kaletra oral solution.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 months	6 months	Waived	
Comments: Capsule formulation not appropriate for this age group. This age group will be studied under NDA 21-251, Kaletra oral solution.			
6 months	12 years	Completed	
12 years	16 years	Deferred	7/1/04
Comments: Studies in adolescents have not been completed. Studies including this age range are in development in collaboration with the Pediatric ACTG. Deferral for this age group also applies to NDA 21-251, Kaletra oral solution.			

This page was last edited on 1/18/02

/S/ 1/18/02

Signature Date

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

NDA Number:	021251	**Trade Name:**	KALETRA
Supplement Number:	004	**Generic Name:**	LOPINAVIR; RITONAVIR
Supplement Type:	SE8	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF HIV

Original NDA Action Date: 7/13/01

Indication # 1 Treatment of HIV infection

Comments (if any): 1/17/02 - Supplement contains extended 48 week safety and efficacy results from pediatric clinical trial.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
6 months	12 years	Completed	
0 months	6 months	Deferred	7/1/04

Comments: A study of Kaletra PK and safety in very young infants (neonates to 6 months of age) is in development in collaboration with the Pediatric ACTG.

12 years	16 years	Deferred	7/1/04

Comments: Studies in this age group have not been completed at this time. At least 2 studies including this age range are in development in collaboration with the Pediatric ACTG. Deferral for this age group also applies to NDA 21-226 for Kaletra capsules.

This page was last edited on 1/18/02

/S/ _____ 1/18/02

Signature Date

CERTIFICATION REQUIREMENT FOR ALL APPLICATIONS FOR APPROVAL OF A DRUG PRODUCT

Per Section 314.70(a) of the Code of Federal Regulations, "Except for a foreign applicant, the applicant shall include a statement certifying that the field copy of the application has been provided to the applicant's home FDA district office".

We certify that the field copy is a "true" copy of the technical section contained in the archival and review copies of the above referenced NDA and has been submitted to Abbott Laboratories' home FDA district office.

Rebecca Welch

Rebecca Welch
Associate Director
Pharmaceutical Products Division
Abbott Laboratories
Abbott Park, Illinois

3/31/00
Date

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/15/02

FROM: Jeffrey S. Murray M.D., M.P.H.
Division of Antiviral Drug Products

SUBJECT: Group Leader's memorandum for NDA 21-226 (KALETRA, lopinavir/ritonavir capsules) and NDA 21-251 (KALETRA, lopinavir/ritonavir oral solution); clinical efficacy supplements S-003 and S-004

TO: HFD-530/Division files

Kaletra is a combination product of two protease inhibitors (PI), lopinavir and ritonavir; the lopinavir component provides the antiviral effect while ritonavir provides increased concentrations of lopinavir via competitive metabolic inhibition of CYP3A. Kaletra capsules and Kaletra oral solution were approved for the treatment of HIV infection in September 2000. Subsequently, Abbott submitted two clinical efficacy supplements to the Kaletra capsules and solution NDAs. These supplements contain longer-term safety and efficacy data (through 48 weeks) on three studies submitted in the original NDAs. Analyses of 48 week data from studies 863 and 957, in treatment naïve and multiple PI experienced patients, respectively, were submitted to NDA 21-226 and 48 week safety and efficacy data from pediatric study 940 were submitted to NDA 21-251. The 48-week analyses of pivotal study 863 partially fulfill Abbott's accelerated approval commitments. Forty-eight week data from a second phase 3 study in treatment experienced adults will be submitted soon for traditional approval of Kaletra.

These three studies demonstrate that Kaletra is safe and effective for the treatment of antiretroviral naïve and experienced adults and children (as young as 6 months of age). In study 863, Kaletra was superior to nelfinavir with respect to the proportion of patients with HIV RNA < 400 copies sustained through 48 weeks of treatment. The superiority of Kaletra was most apparent in patients with higher baseline HIV RNA levels (i.e., differences diverged past 30,000 copies/mL). Study 957 evaluated two doses of Kaletra in combination with efavirenz and nucleoside reverse transcriptase inhibitors. During this trial, after 24 weeks of treatment, all patients were switched to the higher Kaletra dose based on pharmacokinetic and activity data. Treatment response was directly correlated with baseline phenotypic susceptibility in this study. Study 940 evaluated Kaletra in combination with NRTI or NNRTI/NRTI in treatment naïve and experienced children, respectively. Response rates observed at 24 weeks in all three studies were only slightly diminished by 48 weeks of treatment. Please refer to the clinical review written by Kimberly Struble, PharmD for details regarding the safety and efficacy of the adult studies and the clinical review written by Linda Lewis M.D. for details regarding the pediatric study. I completely concur with their analyses and conclusions as stated in their reviews of these supplements.

Therefore, these supplements support the inclusion of longer-term follow-up of safety and efficacy from study 863, displayed in the Description of Clinical Studies section and Adverse Reactions section of the label, study 957 referenced in the Resistance/Cross-Resistance subsections (under the Clinical Pharmacology/Microbiology section of the label) and study 940 which is summarized in the Pediatric Use subsection and also the Adverse Reactions section of the label.

In addition, review of clinical trial safety data and postmarketing reports prompted strengthening on the Precautions section of the label addressing the use of Kaletra in patients with hepatic impairment. An additional statement was added which references postmarketing cases of hepatic decompensation in patients with hepatitis B or C after initiation of Kaletra. Although these cases were confounded by baseline disease, multiple concomitant medications, and advanced HIV disease, physicians are encouraged to consider increased monitoring of such patients after initiating Kaletra.

Another potential issue that emerged with evaluation of the additional follow-up data was a lower rate of treatment response in Black compared to Caucasian adult patients in study 863. As mentioned in Dr. Struble's review, this difference appeared to be driven by a higher rate of treatment discontinuations among Blacks for reasons other than adverse events. This was not observed on the nelfinavir arm. However, safety and tolerability in this study was similar (all event grades and causality) between Blacks and Caucasians. In fact, gastrointestinal events, which are among the most common Kaletra associated clinical events, were slightly higher among Caucasians. Race differences in pediatric patients were not observed, although this may have been confounded by prior antiretroviral therapy at baseline. Given that this issue is unresolved, we have asked Abbott to evaluate, as a postmarketing commitment, race differences in all of their clinical studies including their second phase 3 study (888) to be submitted this calendar year in support of traditional approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray
1/22/02 11:45:21 AM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: December 5, 2001

APPLICATION NUMBER: NDA 21-226 & 21-251, Kaletra (lopinavir/ritonavir) Capsules and Solution

BETWEEN:

Name: Eugene Sun, M.D., Clinical
Marty King, Ph.D., Statistics
Paul Cernohous, Ph.D., Statistics
Greg Bosco, Regulatory
Becky Welch, Regulatory

Phone: 847-937-8971
Representing: Abbott Laboratories

AND

Name: Sean J. Belouin, R.Ph, Regulatory Project Manager
Jeff Murray, M.D., M.P.H., Medical Team Leader
Kim Struble, PharmD., Regulatory Review Officer
Greg Soon, Ph.D., Statistical Team Leader
Rafia Bhore, Ph.D., Statistician

Representing: Division of Antiviral Drug Products (DAVDP), HFD-530

SUBJECT: Clarifications to Virologic Failure Categories

BACKGROUND AND SUMMARY OF TELEPHONE CONVERSATION

Abbott requested clarifications regarding the virologic failure categories outlined in the fax they received from DAVDP on November 21, 2001. The following questions are from Abbott Laboratories with responses from DAVDP.

1. It is possible for subjects to meet virologic rebound criteria but to demonstrate viral resuppression (with no regimen switch) and have HIV RNA <400 copies/mL at Week 48. Our reading of the algorithm indicates that these subjects are to be categorized in the "Rebound" category. Our question is regarding the heading "HIV RNA >400 copies/mL" - we want to clarify that these 'rebound-resuppress' subjects are to be cateogrized under "Rebound" despite the minor paradox that at Week 48 they have HIV RNA <400 but are in a category titled "HIV RNA >400."

DAVDP Response: Regarding virologic rebound, the Division is reevaluating the current algorithm. The sponsor should calculate the data in the tables both ways, for HIV RNA <400 copies/mL at Week 48 and HIV RNA > 400 copies/mL.

The sponsor was asked to provide a list of patients that they felt might be inappropriately classified as virologic failures according to the algorithm. For example, patients who interrupt study drug for adverse events unrelated to study drug and experience HIV RNA > 400 copies/mL but then resuppress to < 400 copies/mL or patients who rebound then resuppress without a change in antiretrovirals.

2. Does the category "Never suppressed through Week 48" refer only to subjects who were on study for 48 weeks (i.e., subjects who did not discontinue) but who never achieved HIV RNA <400 copies/mL?

DAVDP Response: Yes

3. Regarding subjects who never achieve confirmed HIV RNA <400 copies/mL (as described in #2 on the final page of the fax): it is clear that these subjects are to be considered failures at day 0. Should their category for Table 1 (below #5 on the 4th page of the fax) be based on their investigator-specified reason for discontinuation?

   For example, suppose subjects A, B, and C all discontinue at Week 24, and none of them ever demonstrated HIV RNA <400 copies/mL. Subject A discontinues due to an adverse event, Subject B discontinues due to virologic failure, and Subject C is lost to follow-up. Then if the answer to question 3 is "yes," we would categorize A under "Discontinued due to adverse events," B under "Switch due to virologic failure" and C under "Discontinued due to other reasons-->Loss to follow" Are these correct?

DAVDP Response: Yes

4. The fourth question is on analyses to be conducted at <50 copies/mL and applies only to study M98-863, since the other studies did not have the ultrasensitive assay performed regularly.

   On page 2 of the fax, it states, "Perform the following efficacy calculations using LOQ= [redacted] and then LOQ= [redacted]" Then on page 4 of the fax, in #7, it states, "Obtain the proportion <50 copies/mL using the same algorithm."

   The former statement suggests that all listed analyses are to be performed at the 50 copies/mL level, while the latter suggests that only the proportion <50 copies/mL need be determined (i.e., that the Kaplan-Meier analysis and the disposition table need not be performed/created).

   If all analyses are to be performed, some complications should be noted. Since ultrasensitive testing was not performed prior to Week 24, no patient can demonstrate a loss of response after baseline but before Week 24, and the Kaplan-Meier curve is correspondingly flat

between baseline and Week 24. In the disposition table (as in the example shown below #5 on page 4 of the fax), the distribution of reasons for non-responders is somewhat different due to the timing of ultrasensitive testing. (E.g., a patient rebounding at Week 20 in the 400 copies/mL analysis would be a failure at day 0 in the 50 copies/mL analysis since the patient was never tested by the 50-copy assay (and hence was never a responder at 50 copies/mL. If 2 separate disposition tables are to be included in the label, say, differences like this could lead to confusion on the part of a reader.)

Our preference would be simply to calculate the proportion responding at the <50 copies/mL level at Week 48 (as we infer from #7 on page 4). A comparison to the current (August 2001) Sustiva label suggests that this approach is appropriate, but we seek clarification as to whether this is the correct interpretation.

DAVDP Response: The Division expressed that the less than 50 copies/mL algorithm can't be used. There isn't sufficient data before week 24. One can only look at a 'snap shot' at week 48 of the proportion of responders less than 50 copies/mL.

5. In the disposition table (Table 1 below #5 on page 4), under "Discontinued for other reasons," we are planning to include only the categories that appear on the study discontinuation CRF. For example, "Pregnancy" is not a category included on the CRF, so we would not plan to include it in the disposition table. We want to confirm that this approach is appropriate.

DAVDP Response: Yes, that is acceptable.

/S/

Sean J. Bélouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 21, 2001

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Efficacy analyses using the new Time to Loss-of-Virologic Response algorithm

Total no. of pages including cover: 5

Comments: The following statistical comments are being provided on behalf of Rafia Bhore, Ph.D., and Kim Struble, PharmD.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 21, 2001

To: Rebecca A. Welch, Associate Director, PPD Regulatory Affairs

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

From: Sean J. Belouin, R.Ph., Regulatory Project Manager, HFD-530

Through: Rafia Bhore, Ph.D., Statistical Reviewr,HFD-530
Greg Soon, Ph.D., Statistical Team Leader, HFD-530
Kim Struble, PharmD., Regulatory Review Officer, HFD-530
Jeff Murray, M.D., M.P.H., Medical Team Leader, HFD-530

NDA: 20-226: Supplement 003
20-251: Supplement 003

Subject: Efficacy analyses using the new Time to Loss-of-Virologic Response algorithm

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The following statistical comments are being provided on behalf of Rafia Bhore, Ph.D., and Kim Struble, PharmD:

Due to a recent modification of the definition of viral failure by the Division of Antiviral Drug Products (DAVDP), we request the following efficacy analyses using the new Time to Loss-of-Virologic Response algorithm (see below).

Please send the request by December 14, 2001. In order to save time, you may send the results electronically first.

Perform the following calculations using LOQ=— and then LOQ=—

Please conduct the following efficacy analyses:

1. For Study M98-863, calculate time to loss-of-virologic response based on the attached algorithm and plot the survival curves through Week 48 and beyond (similar to Figure 11.4e of Clinical Study Report for M98-863).

2. For any visit, subjects with the following events before or at the visit will be regarded as failures for that visit (see details in attached algorithm):

   a) Death

   b) Permanent discontinuation of the study medication

   c) Switching of study medications

   d) Loss to follow up

   e) Have not achieved confirmed <LOQ status or achieved confirmed <LOQ status but rebounded

   Other subjects will be regarded as responders. Therefore, responders are those who have achieved confirmed viral load <LOQ before the visit of interest but have not become a virologic failure yet.

   Please calculate the response rate for each visit up until Week 48.

3. Plot the response rates over time for the Kaletra™ arm and nelfinavir arm (similar to Figure 2 in Kaletra™ label). We recommend adding the name of the treatment arm next to the curve instead of within a legend (e.g., KALETRA+d4T+3TC and nelfinavir+d4T+3TC). In addition, display the number of patients with evaluation below the x-axis for each treatment arm at each time point.

4. Classify Week 48 failures according to the primary reason for the earliest failure.

APPEARS THIS WAY
ON ORIGINAL

5. Display the information in Step 4 in a table format shown below (similar to Table 3: Outcomes of Randomized Treatment Through Week 48 [Study 863] shown in Kaletra™ label). Also provide p-value for difference in proportion < 400 copies/mL.

Table 1

Outcome	KALETRA+d4T+3TC (n=326)		nelfinavir+d4T+3TC (n=327)	
	n	%	n	%
HIV RNA <400 copies/mL [1]	xxx	(xx%)	xxx	(xx%)
HIV RNA ≥400 copies/mL [2]	xx	(xx%)	xx	(xx%)
Rebound				
Never suppressed through week 48				
Switch due to virologic failure [3]				
Death	xx	(xx%)	xx	(xx%)
Discontinued due to adverse events	xx	(xx%)	xx	(xx%)
Discontinued due to other reasons [4]	xx	(xx%)	xx	(xx%)
Consent withdrawn				
Loss to follow				
Non-compliance				
Pregnancy				
Protocol violation				
Other				
Never treated				

1 p-value= ...

2 Includes ....

3 Switches of study drug are regarded as discontinuations in all other cases.

4 Includes ...

6. Also, report all new CDC Class C events in each treatment arm in Study 863 as text within the Kaletra™ label.

7. Obtain the proportion < 50 copies/mL using the same algorithm.

8. Please provide the proportion < 400 copies/mL using the same algorithm for Studies 957 and 940 using steps above.

9. Please submit the programs, datasets, graphs and tables for obtaining the above results.

10. If you have any questions about this request, please contact us as soon as possible.

Time to Loss-of-Virologic-Response Algorithm

For NDAs with 48 week virologic data, one analysis for computing time to virologic failure may be assessed using the following algorithm.

1. In what follows, visit means visit with an observed viral load. All available visits, including off-schedule visits and post Week 48 visits, should be used for the calculation. Data should not be interpolated for visits or time points with missing data.

2. Subjects who never achieved confirmed HIV RNA levels below the assay limit (on two consecutive visits) before any of the following events will be considered to have failed at time 0.
   a) Death
   b) Discontinuation or switching of study medications. Temporary discontinuation or dose reduction of study medications may be ignored. Discontinuation or dose reduction of background therapies in blinded studies can be ignored. The handling of other changes in background therapies should be pre-specified in the protocol and discussed with the division.
   c) Last available visit

3. For all subjects who have confirmed HIV RNA levels below an assay limit, the time to failure is the earliest of the choices below, with modification specified in 4:
   a) Time of the event as described in 2b
   b) Time of loss to follow-up
   c) Time of confirmed levels above an assay limit. Confirmed is define as two consecutive levels greater than an assay limit or one visit greater than an assay limit followed by loss to follow-up.
   d) Time of death.

4. If the time to virologic failure defined above is immediately preceded by a single missing scheduled visit or multiple consecutive missing scheduled visits, then the time of virologic failure is replaced by the time of the first such missing visit.

For open-label studies, algorithms that incorporate other ways of handling missing data or treatment discontinuations may be used for additional sensitivity analyses. For example, sponsors should perform analyses that treat nonprotocol-specified treatment discontinuations as failures in the study arm and as censored at the time of discontinuation in the control arm when exploring sensitivity of the results to potential biases related to an open-label design.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Sean J. Bélouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

11/21/01 10:50
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
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11/21/01 10:48 DAVDP → 918479378002 NO.875 P01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 21, 2001

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Efficacy analyses using the new Time to Loss-of-Virologic Response algorithm

Total no. of pages including cover: 5

Comments: The following statistical comments are being provided on behalf of Rafia Bhore, Ph.D., and Kim Struble, PharmD.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 6, 2001

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Template for Presenting Resistance Data

Total no. of pages including cover: 4

Comments: The following clinical comments are being provided on behalf of Kim Struble, PharmD. and Jeff Murray, M.D., M.P.H.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 6, 2001

To: Rebecca A. Welch, Associate Director, PPD Regulatory Affairs

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

From: Sean J. Belouin, R.Ph., Regulatory Project Manager, HFD-530

Through: Kim Struble, PharmD., Regulatory Review Officer, HFD-530 /S/ 11/6/01
Jeff Murray, M.D., M.P.H., Medical Team Leader, HFD-530 /S/ 11/6/01

NDA: 20-226: Supplement 003
20-251: Supplement 003

Subject: Template for Presenting Resistance Data

The following clinical comments are being provided on behalf of Kim Struble, PharmD and Jeff Murray, M.D., M.P.H.:

TEMPLATE FOR SUBMITTING RESISTANCE DATA.

For each study please construct datasets as SAS transport files containing the following information. Please include one record (row) per patient per isolate (e.g., baseline, failure, and other timepoints). Please include information on all isolates.

For genotype, baseline and follow-up isolates will be on separate records per patient. However please retain phenotypic data, baseline and follow-up data, for every record.

Suggested Column Headings

Patient Data:

1. Patient identification number
2. Isolate (e.g., baseline, follow-up, etc)
3. Time of isolate (e.g., baseline, week 42, week 48, etc)
4. Previous therapeutic agents from the same class as the candidate drug
5. Treatment group

Endpoint Data:

6. HIV RNA (copies/mL) at baseline
7. HIV RNA (copies/mL) at week 24 (or other predefined time-point)
8. HIV RNA (copies/mL) at week 48 (or other predefined time-point)
9. HIV RNA (copies/mL) at time of loss of virologic response
10. Endpoint assessment: Please indicate if data was censored for reasons other than virologic failure (e.g., discontinuation due to adverse event)

Genotypic Data:

11. Genotype information for all the PI or relevant coding region that was sequenced, one amino acid per column. Changes from WT standard sequence indicated (i.e., blanks indicate no change). The information should be given for both candidate drug and all other antiretroviral agents in the regimen.
12. Number of baseline mutations

Example: Note-this example highlights how genotype information should be displayed and does not include all column headings as suggested above.

Patient #	Isolate	V-82	N-83	I-84	I-85	G-86	R-87	N-88	L-89	L-90	# Base Muts
001	BASE			V				S		M/L	7
002	BASE	A/T		V				D		M	2
003	BASE	T		V							5
004	BASE			V						M	8

Protease cleavage sites (+ = WT, - = mutant)

13. p1/p7 protease cleavage site (+ = WT, - = mutant)
14. p7/p1 Gag cleavage sites (+ = WT, - = mutant)

Phenotypic Data:

15. Baseline IC_{50} for candidate drug
16. Baseline IC_{50} for other antiretroviral agents in the regimen, one column/agent
17. Baseline IC_{50} compared to reference strain for candidate drug
18. IC_{50} at time of endpoint assessment or failure for candidate drug

19. IC_{50} at time of endpoint assessment or failure compared to WT or reference strain for candidate drug
20. Change in IC_{50} from baseline at time of endpoint assessment or failure for candidate drug
21. Change in IC_{50} from baseline at time of endpoint assessment or failure for other antiretroviral agents in the regimen, one column/agent
22. Change in IC_{50} relative to WT for all other antiretroviral agents in the regimen (i.e. other than candidate drug, one column/agent
23. Change in IC_{50} relative to WT or reference strain for each of the approved/investigational agent(s) in the same class

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/S/

Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

11/06/01 15:28
ID=DAVDP

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
11/06	00'36"	918479378002	CALLING	04	OK	0000

11/06/01 15:27 DAVDP → 918479378002 NO.846 P01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 6, 2001

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Template for Presenting Resistance Data

Total no. of pages including cover: 4

Comments: The following clinical comments are being provided on behalf of Kim Struble, PharmD. and Jeff Murray, M.D., M.P.H.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: October 16, 2001

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Detailed Summary of Cases

Total no. of pages including cover: 2

Comments: The following clinical comment is being provided on behalf of Kim Struble, PharmD.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 16, 2001

To: Rebecca A. Welch, Associate Director, PPD Regulatory Affairs

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

From: Sean J. Belouin, R.Ph., Regulatory Project Manager, HFD-530

Through: Kim Struble, PharmD., Regulatory Review Officer, HFD-530
Jeff Murray, M.D., M.P.H., Medical Team Leader, HFD-530

NDA: 20-226: Supplement 003
20-251: Supplement 003

Subject: Detailed Summary of Cases

The following clinical comment is being provided on behalf of Kim Struble, PharmD:

Please provide a detailed summary of cases of hemolytic anemia, thrombocytopenia, and thrombotic thrombocytopenic purpura, hepatic failure, renal failure, and rhabdomyolysis reported in any Kaletra phase I/II and III clinical trial or during the postmarketing phase through October 2001.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

10/16/01 09:38
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
10/16	00'22"	918479378002	CALLING	02	OK	0000

10/16/01 09:37 DAVDP → 918479378002 NO.798 D01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: October 16, 2001

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Detailed Summary of Cases

Total no. of pages including cover: 2

Comments: The following clinical comment is being provided on behalf of Kim Struble, PharmD.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: August 27, 2001

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Request for information regarding pediatric compassionate access protocol

Total no. of pages including cover: 2

Comments: The following comment is on behalf of Linda Lewis, M.D., and Jeff Murray, M.D., M.P.H.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 27, 2001

To: Rebecca A. Welch, Associate Director, PPD Regulatory Affairs

Through: Jeff Murray, M.D., M.P.H., Medical Team Leader, HFD-530
Linda Lewis, M.D., Medical Reviewer, HFD-530

NDA's: 21-226 S-004
21-251 S-004

Subject: Request for information regarding pediatric compassionate access protocol

---

The following comment is on behalf of Linda Lewis, M.D., and Jeff Murray, M.D., M.P.H:

1. Please provide the number of children enrolled in the pediatric compassionate access protocol, their geographic distribution and any additional safety data that might have been collected on them from this program.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Sean J. Bélouin, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

08/27/01 11:43
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
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08/27/01 11:42 DAVDP → 918479378002 NO.683 D01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: August 27, 2001

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Request for information regarding pediatric compassionate access protocol

Total no. of pages including cover: 2

Comments: The following comment is on behalf of Linda Lewis, M.D., and Jeff Murray, M.D., M.P.H.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 14, 2002

To: Rebecca A. Welch, Associate Director, PPD Regulatory Affairs

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

From: Sean J. Belouin, R.Ph., Regulatory Project Manager, HFD-530

Through: Melissa Truffa, R.Ph., Regulatory Review Officer, OPDRA

NDA: 21-226: Supplement 003, Supplement 004
21-251: Supplement 003, Supplement 004

Subject: Post Marketing Kaletra Liver Cases

The following post marketing Kaletra liver cases are being presented on behalf of Melissa Truffa, R.Ph., Office of Drug Safety:

CLINICAL POSTMARKETING COMMITMENTS

Originally, ODS thought there were six cases. Three of the six were duplicates. The three cases are presented below:

1. Report dated 28Nov2000: Male patient, age and date of event unknown. A physician from Spain reported via a representative that a male patient received oral abacavir (Ziagen) concurrently with didanosine, stavudine, and "ABT378" for HIV. He was well controlled on the combination until after about 4 weeks when raised laboratory values were noted; GOT and GPT > 1000 and bilirubin 13. All therapy was stopped. The patient had some years previously received didanosine and stavudine without problems. On the follow-up, the reporting physician considered the event related to Kaletra and unrelated to abacavir.

2. Date of Report: 16Jan01: A 35 year old Caucasian male who was HIV and hepatitis B surface antigen positive died of hepatic encephalopathy. The patient started Kaletra on 3Oct00 and died on 12Dec00. Though he had advanced liver disease (bilirubin 1.6, platelets 71,000, albumin 3.2 on 31Oct00), he did not decompensate until after starting Kaletra.

   Apr98, the patient developed acute hepatitis with bilirubin peaking at 18, AST 2149, and ALT 1084. He was on a regimen of lamivudine/delavirdine/nelfinavir. Hepatitis B core antigen was positive during the flare, and his LFT's gradually returned to baseline off all medications.

   He began didanosine/abacavir/efavirenz in Oct98 but discontinued due abacavir hypersensitivity in Dec98. Feb99, he started didanosine/efavirenz/Fortavase, then stopped efavirenz secondary to intolerance in May99. Nov00, he started didanosine/nevirapine/Fortavase, which he stopped sometime prior to Sept00 for unclear reasons. He restarted Kaletra/didanosine/ nevirapine in 03Oct00. On 21Nov00, he presented with ascites and was started on spironolactone. On 06Dec00, he presented to ER with slurred speech, hyperammonemia and worsening liver function. The next day he was comatose, and remained so until death on 12Dec00.

3. Date of the event: 01Feb01: An US physician reported that 45 old male with a history of chronic hepatitis B received abacavir (Ziagen) tablets for the treatment of HIV. Approximately 2 months after initiation of abacavir, the patient felt unwell and complained of abdominal pain and fatigue. He was jaundiced with increased liver function (AST 2313 and ALT 1455 on 21Feb01). The patient also complained of oral thrush and sinusitis. Twenty days after onset of symptoms, the patient was hospitalized and all medications were discontinued. Treatment included supportive care. Eleven days after onset on 04Mar01, the patient died due to fulminant liver failure after a twelve-day hospitalization. An autopsy was performed. The physician did not know if the events were related to hypersensitivity. Concurrent medications included lamivudine, Kaletra, efavirenz, hydroxyurea (all started Dec00 and stopped on 21Feb01).

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/S/

Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

01/14/02 15:19
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01/14/02 15:18 DAVDP → 918479378002 NO.009 P01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 14, 2002

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Post Marketing Kaletra Liver Cases

Total no. of pages including cover 3

Comments: The following post marketing Kaletra liver cases are being presented on behalf of Melissa Troffa, R.Ph., Office of Drug Safety

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 14, 2002

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Post Marketing Commitments and Microbiology labeling edits

Total no. of pages including cover: 5

Comments: The following clinical post marketing commitments and microbiology labeling edits are being provided on behalf of Jeff Murray, M.D., M.P.H., Linda Lewis, M.D., and Julian O'Rear, Ph.D.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **January 14, 2002**

To: **Rebecca A. Welch, Associate Director, PPD Regulatory Affairs**

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

From: **Sean J. Belouin, R.Ph., Regulatory Project Manager, HFD-530**

Through: **Jeff Murray, M.D., M.P.H., Medical Team Leader, HFD-530**
Linda Lewis, M.D., Medical Reviewer, HFD-530
Julian O'Rear, Ph.D., Microbiology Reviewer,HFD-530

NDA: **21-226: Supplement 003, Supplement 004**
21-251: Supplement 003, Supplement 004

Subject: **Post Marketing Commitments and Microbiology labeling edits**

The following clinical post marketing commitments and microbiology labeling edits are being provided on behalf of Jeff Murray, M.D., M.P.H., Linda Lewis, M.D., and Julian O'Rear, Ph.D:

Please update the January 8th, 2002 label and submit an updated label to both Supplements 003 and 004. The label will be approved simultaneously for both, thus the label must be identical for both Supplements.

CLINICAL POSTMARKETING COMMITMENTS

The following postmarketing commitments need to agreed to prior to the approval of Supplements 003 and 004:

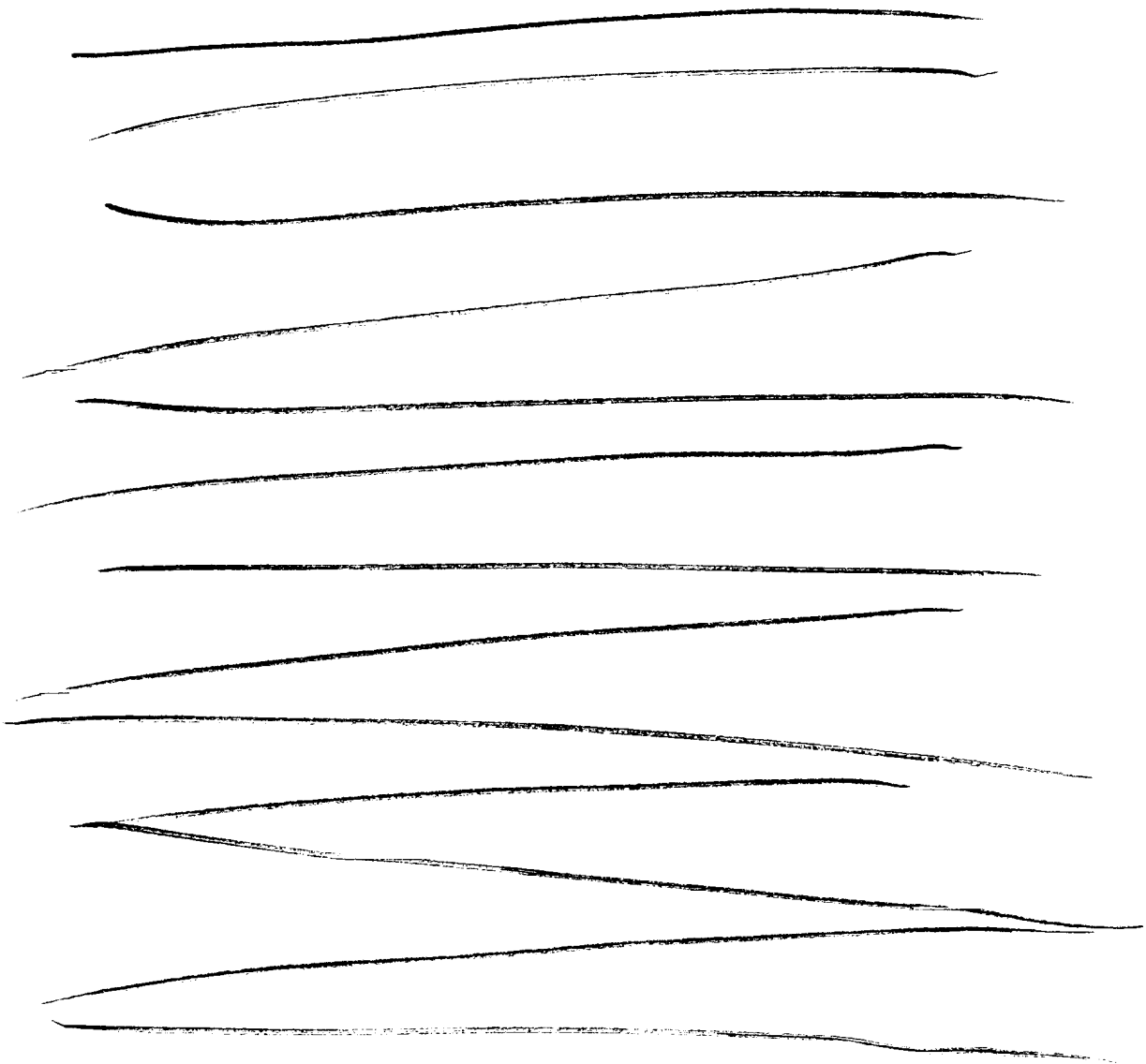
1. Evaluate the relative treatment response, safety and tolerability of Caucasians vs. Blacks using data from study 888 and the entire clinical trial data available to Abbott. Analyses may be submitted at the time of Traditional Approval, projected for first quarter 2002.

2. Kaletra has been shown to be very effective in treatment naïve pediatric patients. Efficacy decreases if children have had previous antiretroviral therapy and decreases most dramatically in those who have had prior therapy with other protease inhibitors (PIs). The U.S. HIV-infected pediatric population has a large proportion of children who have received multiple PIs and have few remaining treatment options. Please evaluate the use of Kaletra in this population of more extensively treated pediatric patients, with special attention to identifying whether the currently approved dosing recommendations are adequate for children who have failed treatment with multiple (≥ 2) other PIs.

MICROBIOLOGY LABELING EDITS:

Deleted text has ~~strike-thru~~ and added text is <u>underlined</u>.

CLINICAL PHARMACOLOGY
Microbiology



1 page(s) of revised draft labeling has been redacted from this portion of the review.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

01/14/02 15:12
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
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1/14/02 15:10 DAVDP → 918479378002 NO.007 D01

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 14, 2002

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Post Marketing Commitments and Microbiology labeling edits

Total no. of pages including cover: 5

Comments: The following clinical post marketing commitments and microbiology labeling edits are being provided on behalf of Jeff Murray, M.D., M.P.H., Linda Lewis, M.D., and Julion O'Rear, Ph.D.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 10, 2002

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Clinical and Statistical labeling comments

Total no. of pages including cover: 4

Comments: The following clinical and statistical comments are being provided on behalf of Jeff Murray, M.D., Linda Lewis, M.D., and Rafia Bhore, Ph.D.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 10, 2002

To: Rebecca A. Welch, Associate Director, PPD Regulatory Affairs

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

From: Sean J. Belouin, R.Ph., Regulatory Project Manager, HFD-530

Through: Jeff Murray, M.D., M.P.H., Medical Team Leader, HFD-530
Linda Lewis, M.D., Medical Reviewer, HFD-530
Rafia Bhore, Ph.D., Statistical Reviewer,HFD-530

NDA: 21-226: Supplement 003, Supplement 004
21-251: Supplement 003, Supplement 004

Subject: Clinical and Statistical labeling comments

The following clinical and statistical comments are being provided on behalf of Jeff Murray, M.D., M.P.H., Linda Lewis, M.D., and Rafia Bhore, Ph.D:

Please update the January 8th, 2002 label and submit an updated label to both Supplements 003 and 004. The label will be approved simultaneously for both, thus the label must be identical for both Supplements.

CLINICAL

Under Description of Clinical Studies for Study 863:

1. The current percentages describing HIV RNA < 400 according to baseline viral load will need to be updated according to the algorithm. The new percentages are 72 and 78 for the greater than and less than 100,000 copies/mL subgroups, respectively. In addition, we would like you to provide more information regarding the subset of patients for which the superiority of KALETRA is most crucial, that is, those with baseline HIV RNA levels >100,000 copies per ml. Although this was an unplanned subgroup analysis, we believe that

clinicians will find this information useful. Our preference is to have this data be inserted in text and table format as shown below:

"Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV RNA <400 copies/mL (75% vs. 62%, respectively) and HIV RNA <50 copies/mL (67% vs. 52%, respectively). This difference between KALETRA and nelfinavir is mainly due to patients with HIV RNA ≥100,000 copies/mL as shown in table below.

Table 1: Proportion of Responders[1] Through Week 48 by Baseline Viral Load (Study 863)

Baseline Viral Load	KALETRA+d4T+3TC % (n)	Nelfinavir+d4T+3TC % (n)
<100,000 HIV RNA copies/mL	78% (167)	74% (168)
≥100,000 HIV RNA copies/mL	72% (159)	50% (159)

[1] Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

Under Precautions:

2. After speaking with Dr. Struble and our colleagues at OPDRA (now called ODS –Office of Drug Safety), we believe the precaution addressing hepatic impairment needs to be strengthened. OPDRA found 35 postmarketing cases of hepatic failure/liver damage. Some of these were submitted through other sponsors (use of concomitant meds) or directly to FDA. Consequently, some of these are not in your postmarketing database. Although, it appears that the vast majority of hepatic failures following treatment with Kaletra occurred in patients with underlying chronic hepatitis (B and/or C), several cases suggest that otherwise "stable" hepatically impaired individuals may have decompensated on Kaletra. Please note that the ritonavir label currently has similar statements. Also it is possible that hepatically impaired individuals receiving Kaletra may potentially have higher concentrations of ritonavir than patients without liver disease. Thus, we believe the following statements should be added to the current precaution.

"KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of KALETRA treatment."

Under Pediatrics: Treatment-Emergent Adverse Events

3. In general the label revisions dated 1/8/02 regarding the pediatric clinical trial of Kaletra are acceptable. However, in the section **Pediatrics: Treatment-Emergent Adverse Events**, please replace the general term "gastrointestinal events" with the more specific terms "nausea", "vomiting" and/or "diarrhea" as appropriate. Gastrointestinal events could include any processes, ranging in severity from nausea or vomiting to bowel obstruction or GI bleeding. The more specific terms will provide pediatric clinicians with an accurate description of the adverse events identified in the clinical trial.

4. Similarly, please select another term for "taste perversion" as this phrase has no clear meaning for pediatric clinicians and does not accurately reflect the patients' complaints. It is understood that this may have been the only COSTART term available for coding purposes but the events described are clearly related to the taste of the drug and its palatability and not to an abnormality of the sense of taste. Two phrases that might more accurately express the complaints are poor palatability and taste aversion.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Sean J. Belouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 10, 2002

To: Rebecca A Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Clinical and Statistical labeling comments

Total no. of pages including cover: 4

Comments: The following clinical and statistical comments are being provided on behalf of Jeff Murray, M.D., M.P.H., Linda Lewis, M.D., and Rafia Bhore, Ph.D.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2002

To: Rebecca A. Welch	**From:** Sean J. Belouin. R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Clinical, Statistical and Microbiology labeling comments

Total no. of pages including cover: 10

Comments: The following clinical, statistical, and microbiology comments are being provided on behalf of

Jeff Murray, M.D., M.P.H., Linda Lewis, M.D., Rafia Bhore, Ph.D., and Julian O'Rear, Ph.D.

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 8, 2002

To: Rebecca A. Welch, Associate Director, PPD Regulatory Affairs

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

From: Sean J. Belouin, R.Ph., Regulatory Project Manager, HFD-530

Through: Jeff Murray, M.D., M.P.H., Medical Team Leader, HFD-530
Linda Lewis, M.D., Medical Reviewer, HFD-530
Rafia Bhore, Ph.D., Statistical Reviewer,HFD-530
Julian O'Rear, Ph.D., Micro Reviewer, HFD-530

NDA: 21-226: Supplement 003, Supplement 004
21-251: Supplement 003, Supplement 004

Subject: Clinical, Statistical and Microbiology labeling comments

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The following clinical, statistical, and microbiology comments are being provided on behalf of Jeff Murray, M.D., M.P.H., Linda Lewis, M.D., Rafia Bhore, Ph.D., and Julian O'Rear, Ph.D:

Please update the May 29th, 2001 label and submit an updated label to both Supplements 003 and 004. The label will be approved simultaneously for both, thus the label must be identical for both Supplements.

CLINICAL

1. In the **Pediatric Use** section, describing the efficacy of Kaletra in the pediatric treatment study (Study 940), we would prefer that you utilize the proportion of patients successfully treated that was generated using the algorithm for treatment success and failure. It is not necessary to include graphs or tables in this section since the number of patients who were considered treatment failures due to reasons other than virologic failure was very small. The description of the 2 children who were discontinued from study is adequate. This could be written as follows:

"Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA < 400 was 80% for antiretroviral naïve patients and 71% for antiretroviral experienced. The mean increase from baseline...."

2. In the **ADVERSE REACTIONS, Pediatrics: Laboratory Abnormalities** section, Table 9, I have several comments. First, it would seem more logical to set the critical value for bilirubin at "> 3 x ULN" rather than "> 2.9 x ULN" since this is the Grade 3 cut-off cited in the protocol toxicity table. This change would not alter the number of patients included in this category. Using an upper limit of ALT >215 U/L (> 5 x ULN) I identified 8 children (8%) above the cut-off value. Using an upper limit of AST > 180 U/L I identified 9 children (9%) above the cut-off value. (Please remind me why a value of > 180 U/L was chosen for this critical value since it does not represent 5 x ULN for any of the documented laboratory reference ranges described in the dataset.) I included in my tabulations children who had critical values on Day 1/Baseline that had not returned to normal by the next visit. I did not include children who had abnormal values only at the time of screening. Similarly, I identified 9 children with amylase values > 2.5 x ULN on Day 1 or later. Most of these children had chronically elevated serum amylase levels throughout the study, but 7 of them (7%) also had elevated pancreatic amylase levels at the time their serum amylase was > 2.5 x ULN. Finally, the footnote detailing the 2 dose levels may be deleted or could be altered to note that after 24 weeks of therapy all patients received 300 mg lopinavir/75 mg ritonavir.

3. The **Pediatrics: Treatment-Emergent Adverse Events** section does not adequately profile the spectrum of adverse events reported during the clinical trial. The patient whose adverse event was designated "hypersensitivity reaction" should be included in the group of patients with moderate to severe rash. Please include a statement that describes how many other patients experienced significant adverse events and identifies the more commonly encountered adverse events. For example:

   "Rash, gastrointestinal events, respiratory system events and complaints about poor drug palatability were among the most commonly reported adverse events in pediatric patients treated with combination therapy including Kaletra for up to 48 weeks in Study 940. A total of 8 children experienced moderate or severe adverse events at least possibly related to Kaletra. Rash (reported in 3%) was the only drug-related clinical adverse event of moderate to severe intensity observed in ≥ 2% of children enrolled."

STATISTICAL

Statistics Labeling Comments for Study 863 in Description of Clinical Studies

1. Remove **Figure 3: Time to Treatment Failure**, from the label

2. For **Figure 2: Treatment Response Through 48 Weeks**, please make the following changes

- Change title to "Virologic Response Through Week 48, Study 863*†" (Refer to footnotes * and † in AGENERASE™ label).
- Suggest using "empty circles" as the symbols for KALETRA+d4T+3TC arm and "solid squares" as symbols for nelfinavir+d4T+3TC. Write the name of the treatment arm next to the corresponding curve (as done in NDA 21-226 and 21-251 correspondence dated December 17, 2001).
- Put a legend for the figure showing the treatment arms as KALETRA + d4T + 3TC (n=326) and nelfinavir + d4T+3TC (n=327). Do not show numbers of subjects with HIV RNA values at each time point below the figure for each treatment group (as done in NDA 21-226 and 21-251 correspondence dated December 17, 2001).
- Change the label of Y-axis to "Proportion of Patients with HIV-1 RNA <400 copies/mL".
- Change the label of X-axis to "Study Week".

3. For **Table 3: Outcomes of Randomized Treatment Through Week 48 (Study 863)**, please make the following changes. Display the table in the label upon these changes.
   - Refer to Table 3 on the next page. Change the names of the outcome categories and update the numbers as shown.

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 3: Outcomes of Randomized Treatment Through Week 48 (Study 863)

Outcome	KALETRA+d4T+3TC (N=326)	Nelfinavir+d4T+3TC (N=327)
Responder*[1]	75%	62%
Virologic failure[2]	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse events	4%	4%
Discontinued due to other reasons[3]	10%	8%

* Corresponds to rates at Week 48 in Figure 2.

1 Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

2 Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.

3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

4. For paragraphs appearing in KALETRA label (dated May 29, 2001) below Table 3:

   - Move paragraph 2 and put it above paragraph 1. Change the words for current paragraph 2 as follows:

     "Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV RNA <400 copies/mL (75% vs. 62%, respectively) and with HIV RNA <50 copies/mL (67% vs. 52%, respectively)."

   - Paragraph 1 regarding response rates by baseline viral load may change in the next version of the label pending further analysis.

   - Paragraph 3 regarding CD4 cell count may remain same.

   - Remove paragraph referring to Figure 3 (which needs to be removed also).

APPEARS THIS WAY
ON ORIGINAL

Explanation of FDA analyses:

The following table shows the Efficacy Outcomes of randomized treatment through Week 48 in Study 863 (for LOQ= [redacted] copies/mL) as obtained by the FDA Statistical Reviewer, using the Time to Loss of Virologic Response algorithm (which was provided earlier by DAVDP/FDA).

Outcomes of Randomized Treatment Through Week 48 (Study 863)

Outcome	KALETRA+d4T+3TC (N=326)	Nelfinavir+d4T+3TC (N=327)
	n (%)	n (%)
HIV RNA <400 copies/mL	**246 (75%)**	**204 (62%)**
HIV RNA ≥400 copies/mL	**28 (9%)**	**81 (25%)**
Rebound	22 (7%)	50 (15%)
Never suppressed through Week 48	6 (2%)	31 (9%)
Death	**5 (2%)**	**2 (1%)**
Discontinued due to adverse events	**14 (4%)**	**13 (4%)**
Discontinued due to other reasons	**33 (10%)**	**27 (8%)**
Consent withdrawn (Personal reasons)	7 (2%)	6 (2%)
Loss to follow	12 (4%)	15 (5%)
Non-compliance	8 (2%)	5 (2%)
Protocol violation (Required prohibited medication)	1 (<1%)	0 (0%)
Other	5 (2%)	1 (<1%)
Total	**326 (100%)**	**327 (100%)**

There are a few differences in numbers between the above table and the corresponding table provided by Abbott, in the correspondence dated December 17, 2001 for NDA 21-226 and 21-251. The differences in numbers are explained as follows.

1. Success (HIV RNA <400 copies/mL) category:

   a) The patients classified as Successes in the KALETRA™ arm as obtained by the Statistical Reviewer were identical to those provided by Abbott.

   b) In the nelfinavir treatment arm, we classified patient 3558 as a "Rebound" because at Week 40 the viral load of this patient was 470 copies/mL and at Week 48, the viral load was exactly 400 copies/mL. This is a confirmed failure. Hence the patient has "rebound".

2. Virologic Failure (HIV RNA ≥400 copies/mL) category:

   a) The reason of discontinuation which was coded as "discontinued due to virologic failure" in the database was ignored. Instead classification for virologic failure was based on the subcategories of "Rebound" or "Never suppressed through Week 48".

   b) In the KALETRA™ arm, the differences were due to 4 patients 3122, 3681, 3243, and 3601. These patients were suppressed through their last visit (which occurred before Week 48) and discontinued the study thereafter. Therefore, their outcome should be classified as "Discontinuation due to [the appropriate reason]" and not as "Viral Rebound".

   c) In the nelfinavir arm, the differences were due to 5 patients 3525, 3063, 3368, 3495, and 3442 who were suppressed through their last visit and then discontinued the study, and also due to 2 patients 3558 and 3434. Patient 3558 is classified as rebound, as explained above in Step 1 b. Patient 3434 rebound only at the last visit before discontinuation. Hence a rebound.

   d) Additionally, 4 patients 3379, 3208, 3262, and 3115, in the nelfinavir arm were classified as rebounds by Abbott. These patients were never confirmed to be successes on two consecutive visits. Therefore they should be correctly classified as "Never suppressed through Week 48".

3. Death category:

   All the patients matched in the efficacy outcome category of death. There were 5 patients (3317, 3191, 3307, 3163, and 3651) in the KALETRA™ arm and 2 patients (3364, 3422) in the nelfinavir arm whose efficacy outcome was attributed to death.

   There were 2 additional deaths in the study. Patient 3462 in the nelfinavir arm had a viral rebound first and later died. The efficacy outcome of this patient was Viral Rebound. Another patient who died was patient 3615 who was never treated.

4. Discontinued due to adverse events category:

   All the patients matched in the category of discontinued due to adverse events. Patient 3133 was assigned as discontinued due to adverse event per the algorithm. The discontinuation happened in the Week 48 window.

5. Discontinued due to other reasons category:

   The mismatches of patients in this category are due to the patients 3122, 3681, 3525, 3243, 3601, 3063, 3368, 3495, 3434, and 3442, as explained in Steps 2 b) and 2 c) of Virologic failure category.

   Note that patients 3122, 3087, and 3243 were coded as discontinuation due to other reason, but had also withdrawn consent according to a comment. Patient 3648 was coded as discontinuation due to other reason, but was also coded as non-compliant. So reclassify patient 3648 to non-compliant category.

MICROBIOLOGY

Strike thru is ~~deleted~~ and addition is <u>underlined</u>.

Microbiology

Mechanism of action: Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral activity in vitro: The *in vitro* antiviral activity of lopinavir against laboratory HIV strains and clinical HIV isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) of lopinavir against five different HIV-1 laboratory strains ranged from 10-27 nM (0.006 – 0.017 μg/mL, 1 μg/mL = 1.6 μM) and ranged from 4-11 nM (0.003 – 0.007 μg/mL) against several HIV-1 clinical isolates (n=6). In the presence of 50% human serum, the mean EC_{50} of lopinavir against these five laboratory strains ranged from 65 – 289 nM (0.04 – 0.18 μg/mL), representing a 7- to 11-fold attenuation. Combination drug activity studie with lopinavir and other protease inhibitors or reverse transcriptase inhibitors have not been completed.

Resistance: HIV-1 isolates with reduced susceptibility to lopinavir have been selected *in vitro*. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses *in vitro*.

The selection of resistance to KALETRA in antiretroviral treatment naive patients has not y been characterized. In a Phase III study in 653 antiretroviral treatment naive patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV >400 copies/mL at Week 24, 32, 40 and/or 48 were analyzed. Evidence of ~~genotypic or phenotypic~~ resistance to KALETRA was observed in 0/37 (0%) of <u>evaluable</u> KALETRA-treated patients. Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of <u>evaluable</u> nelfinavir-treated patients. <u>The selection of resistance to KALETRA in antiretroviral treatment naïve pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).</u>

Resistance to KALETRA has been noted to emerge in patients treated with other protease inhibitors prior to KALETRA therapy. In Phase II studies of 227 antiretroviral treatment naive and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (>400 copies/mL) viral RNA following treatment with KALETRA for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (nelfinavir, indinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, saquinavir and ritonavir). All four of these patients had at least 4 mutations associated with protease inhibitor resistance immediately prior to KALETRA therapy. Following viral rebound, isolates from these patients all contained additional mutations, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify lopinavir-associated mutational patterns in isolates from patients on KALETRA therapy. The assessment of these mutational patterns is under study.

Cross-resistance - Preclinical Studies: Varying degrees of cross-resistance have been observed among protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during KALETRA therapy.

The *in vitro* activity of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed >4-fold reduced susceptibility to nelfinavir (n=13) and saquinavir (n=4), displayed <4-fold reduced susceptibility to lopinavir. Isolates with >4-fold reduced susceptibility to indinavir (n=16) and ritonavir (n=3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies - Antiviral activity of KALETRA in patients with previous protease inhibitor therapies ~~therapy~~. The clinical relevance of reduced *in vitro* susceptibility to lopinavir has been examined by assessing the virologic response to KALETRA therapy with respect to baseline viral genotype and phenotype, in 56 NNRTI-naive patients with HIV RNA >1000 copies/mL despite previous therapy with at least two protease inhibitors selected from nelfinavir, indinavir, saquinavir and ritonavir (Study 957). In this study patients were initially randomized to receive one of two doses of KALETRA in combination with efavirenz and nucleoside reverse transcriptase inhibitors. The EC_{50} of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold higher than the EC_{50} against wild type HIV. Fifty-five percent (31/56) of these baseline isolates displayed a >4-fold reduced susceptibility to lopinavir. These 31 isolates had a mean reduction in lopinavir susceptibility of 27.9-fold. Table 1 shows the 48 week virologic response (HIV RNA < 400 and < 50 copies) according to susceptibility and number of genotypic mutations at baseline in 50 evaluable patients enrolled in the study (957) described above. Because this was a select patient population and the sample size was small, the data depicted in Table 1 do not constitute definitive clinical susceptibility breakpoints. Additional data are needed to determine clinically significant breakpoints for KALETRA.

Table 1: HIV RNA Response at Week 48 by baseline KALETRA susceptibility and by number of PI-associated mutations[1]

KALETRA Susceptibility[2] at baseline	HIV RNA < 400 copies/mL (%)	HIV RNA < 50 copies/mL (%)
< 10 fold	25/27 (93%)	22/27 (81%)
>10 and < 40 fold	11/15 (73%)	9/15 (60%)
≥ 40 fold	2/8 (25%)	2/8 (25%)
Number of PI mutations at baseline		
Up to 5	21/23 (91%)[3]	19/23 (83%)
>5	17/27 (63%)	14/27 (52%)

[1] KALETRA susceptibility was determined by recombinant phenotypic technology performed by Virologic; genotype also performed by Virologic

[2] Fold change in susceptibility from wild type

[3] Thirteen of the 23 patient isolates contained PI mutations at positions 82, 84, and/or 90

~~After 24 48 weeks of treatment with KALETRA, efavirenz and nucleoside reverse transcriptase inhibitors, plasma HIV RNA ≤400 copies/mL was observed in 93% (25/27), 73% (11/15), and 25% (2/8) of patients with <10 fold, 10- to 40-fold, and ≥40-fold reduced susceptibility to lopinavir at baseline, respectively. Plasma HIV RNA ≤50 copies/mL was~~

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Sean J. Bélouin, R.Ph
Regulatory Project Manager
Division of Antiviral Drug Products

MESSAGE CONFIRMATION

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2002

To: Rebecca A Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Clinical, Statistical and Microbiology labeling comments

Total no. of pages including cover: 10

Comments: The following clinical, statistical, and microbiology comments are being provided on behalf of Jeff Murray, M.D., M.P.H., Linda Lewis, M.D., Rafia Bhore, Ph.D., and Julian O'Rear, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF 45 DAY FILING MEETING MINUTES

NDA: 21-226/SE8-004
21-251/SE8-004

DATE: 27 August 2001

DRUG: Kaletra® (lopinavir/ritonavir)

INDICATION: Treatment of HIV-1 Infection

SPONSOR: Abbott Pharmaceuticals, Inc.

PARTICIPANTS: Debra Birnkrant, M.D., Acting Division Director, HFD-530
Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530
Linda Lewis, M.D., Medical Reviewer, HFD-530
Kim Struble, PharmD., Regulatory Review Officer, HFD-530
Greg Soon, Ph.D., Statistical Team Leader, HFD-530
Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader, HFD-530
Jooran Kim, PharmD., Clinical Pharmacology, HFD-530
Sean Belouin, R.Ph., Regulatory Project Manager, HFD-530

Related Documents: ———

BACKGROUND: Kaletra (lopinavir/ritonavir), submitted by Abbott Pharmaceuticals, Inc., was granted approval for the 133.3/33.3 mg lopinavir/ritonavir capsule and 80/20 mg/mL lopinavir/ritonavir oral solution on September 15, 2000 (under subpart H). Abbott Pharmaceuticals, Inc., submitted this current supplemental NDA on July 12, 2001 which consists of the 48-week study report for study M98-940, which is the Kaletra Pediatric Study. Also included is modified adverse event rates based on the 48-week results. The applicant has paid the appropriate user fee with the original NDA application dated **May 31, 2000** when 24-week data was submitted. No user fee is required with this 48-week update. The necessary financial disclosure documentation was included with the original NDA dated May 31, 2000. This application has been granted a standard review with an action date of May 13, 2002. However, it will be the goal of the review team to take action on this supplement in conjunction with Supplement 003 (which contains efficacy, safety and virology data from studies M98-863 and M98-957) on or no later than January 18, 2001. This meeting was held to determine whether this application was fileable.

DISCUSSIONS:

1. **Statistics**

   Dr. Soon concluded that this application was fileable with no statistical issues.

2. **Microbiology**

   No microbiology data was reviewed with initial submission. Follow-up data will be submitted regarding resistance data. A review of this will be required.

3. **Clinical**

   Dr. Lewis concluded that this application was fileable. One comment requesting information from Study 98-940 will be faxed to the applicant. Additionally, Dr. Struble indicated that resistance data will need to be reviewed by the microbiology reviewer.

4. **Clinical Pharmacology and Biopharmaceutics**

   Not applicable. No clinical pharmacology and biopharmaceutics data being reviewed for this application.

5. **Pharmacology/Toxicology**

   Not applicable. No pharmacology/toxicology data being reviewed for this application

6. **Chemistry**

   Not applicable. No chemistry data being reviewed for this application.

CONCLUSION

The review team concluded that sNDA 21-226/SE8-004 and 21-251/SE8-004 was fileable. The applicant will be notified of the application's fileability and PDUFA action date.

ACTION ITEMS

None

Signature, minutes preparer: /S/

Date: 8/30/2001

Concurrence:

HFD-530/ActingDivDir/Birnkrant- /S/ 8/29/01
HFD-530/MOTL/Murray- 8/28/01
HFD-530/MO/Lewis- 8/27/01
HFD-530/RRO/Struble- /S/ 8/27/01
HFD-530/BiopharmTL/Reynolds- 8/27/01
HFD-530/Biopharm/Kim- /S/ 8/27/01
HFD-530/StatsTL/Soon-

Cc:

NDA 21-226 SE8-004
NDA 21-251 SE8-004
Division File
HFD-530/ActingDivDir/Birnkrant
HFD-530/CRPM/DeCicco
HFD-530/MOTL/Murray
HFD-530/MO/Lewis
HFD-530/RRO/Struble
HFD-530/ActingMicroTL/Mishra-
HFD-530/MicroTL/O'Rear
HFD-530/StatsTL/Soon
HFD-530/PharmtoxTL/Farrelly
HFD-530/Pharmtox/Zhang
HFD-530/BiopharmTL/Reynolds
HFD-530/Biopharm/KimJ
HFD-530/ChemTL/Miller
HFD-530/Chem/Lo
HFD-530/RPM/Belouin

45 Day Filing Meeting

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF 45 DAY FILING MEETING MINUTES

NDA: 21-226/SE8-003
21-251/SE8-003

DATE: 2 May 2001

DRUG: Kaletra® (lopinavir/ritonavir)

INDICATION: Treatment of HIV-1 Infection

SPONSOR: Abbott Pharmaceuticals, Inc.

PARTICIPANTS: Debra Birnkrant, M.D., Acting Division Director, HFD-530
Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530
Kim Struble, PharmD., Regulatory Review Officer, HFD-530
Greg Soon, Ph.D., Statistical Team Leader, HFD-530
Julian O'Rear, Ph.D., Microbiology Team Leader, HFD-530
Kellie Reynolds, PharmD., Clinical Pharmacology Team Leader, HFD-530
Jooran Kim, PharmD., Clinical Pharmacology, HFD-530
Hao Zhang, Ph.D., Pharmacology/Toxicology, HFD-530
Tony DeCicco, R.Ph., Chief Regulatory Project Manager, HFD-530
Sean Belouin, R.Ph., Regulatory Project Manager, HFD-530

Related Documents: [redacted]

BACKGROUND: Kaletra (lopinavir/ritonavir), submitted by Abbott Pharmaceuticals, Inc., was granted approval for the 133.3/33.3 mg lopinavir/ritonavir capsule and 80/20 mg/mL lopinavir/ritonavir oral solution on September 15, 2000 (under subpart H). Abbott Pharmaceuticals, Inc., submitted this current supplemental NDA on March 19, 2001 which provides for updated 48 week efficacy, safety and virology data from studies M98-863 and M98-957. The applicant has paid the appropriate user fee with the original NDA application dated May 31, 2000 when 24-week data was submitted. No user fee is required with this 48-week update. The necessary financial disclosure documentation was included with the original NDA dated May 31, 2000. This application has been granted a standard review with an action date of January 18, 2001. This meeting was held to determine whether this application was fileable.

DISCUSSIONS:

1. **Statistics**

Dr. Soon concluded that this application was fileable.

2. **Microbiology**

   Dr. O'Rear concluded that this application was fileable.

3. **Clinical**

   Dr. Struble concluded that this application was fileable.

4. **Clinical Pharmacology and Biopharmaceutics**

   Not applicable. No clinical pharmacology and biopharmaceutics data being reviewed for this application.

5. **Pharmacology/Toxicology**

   Not applicable. No pharmacology/toxicology data being reviewed for this application

6. **Chemistry**

   Not applicable. No chemistry data being reviewed for this application.

CONCLUSION

The review team concluded that sNDA 21-226/SE8-003 and 21-251/SE8-003 was fileable. The applicant will be notified of the application's fileability and PDUFA action date.

ACTION ITEMS

None

Signature, minutes preparer: /S/

Date: 5/3/2001

Concurrence:

HFD-530/ActingDivDir/Birnkrant- /S/ 5/15/01
HFD-530/CRPM/DeCicco 5-7-01
HFD-530/MOTL/Murray- /S/ 5/15/01
HFD-530/RRO/Struble- 5/15/01
HFD-530/MicroTL/O'Rear- /S/ 5/7/01
HFD-530/StatsTL/Soon- 5/4/01

Cc:

NDA 21-226 SE8-003
NDA 21-251 SE8-003
Division File
HFD-530/ActingDivDir/Birnkrant
HFD-530/CRPM/DeCicco
HFD-530/MOTL/Murray
HFD-530/RRO/Struble
HFD-530/MicroTL/O'Rear
HFD-530/StatsTL/Soon
HFD-530/PharmtoxTL/Farrelly
HFD-530/Pharmtox/Zhang
HFD-530/BiopharmTL/Reynolds
HFD-530/Biopharm/KimJ
HFD-530/ChemTL/Miller
HFD-530/Chem/Lo
HFD-530/RPM/Belouin

45 Day Filing Meeting

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 14, 2002

To: Rebecca A. Welch	**From:** Sean J. Belouin, R.Ph
Company: Abbott Laboratories	Division of Antiviral Drug Products
Fax number: 847-937-8002	**Fax number:** 301-827-2523
Phone number: 847-937-8971	**Phone number:** 301-827-2481

Subject: Post Marketing Kaletra Liver Cases

Total no. of pages including cover: 3

Comments: The following post marketing Kaletra liver cases are being presented on behalf of Melissa Truffa, R.Ph., Office of Drug Safety

Document to be mailed: ☐ YES ☑ NO

January 15, 2002

Division of Anti-Viral Drug Products, HFD-530
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
1st Floor Document Control Room
Rockville, Maryland 20850

Re: KALETRA (ABT-378)
NDA 21-226 and 21-251

Amendment to Supplement
Supplements 003 and 004

Dear Madam or Sir:

The sponsor, Abbott Laboratories, submits the following information as an amendment to Supplements 003 and 004 under KALETRA NDAs 21-226 and 21-251. These amendments contain the most recent label revision incorporating the information sent in the facsimiles received January 10, January 14 and discussed during a teleconference on January 15, 2002. In addition, these amendments contain a response to the two Phase IV commitments identified in a facsimile sent on January 14, 2002. Finally, a financial disclosure for the 48 week data for clinical studies M98-863, M98-957 and M98-940 submitted under supplement 003 and 004 are provided.

If you have any questions regarding this data, please contact me at the number provided below. Thank you for your consideration of this matter.

Sincerely,

Rebecca A. Welch
Director
PPD Regulatory Affairs
847-937-8971

Phase IV Commitments

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 Caucasions 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 (≥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.