CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226

21-251

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY CHECKLIST

Exclusivity Summary for: NDA # 21-226-21-251 SUPPL #

Trade Name Kaletra

Generic Name Lopinavir / Ritonavir

Applicant Name Abbott Laboratories Division 530

Project Manager Sylvia Lynche Approval Date 9-15-00

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

   b. Is it an effectiveness supplement? ..... ☐ Yes ☐ No

      If yes, what type? (SE1, SE2, etc.)? _____

   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 ☐ 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 exclusity? ..... ☐ Yes ☑ No

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

If you have answered "No" to <u>all</u> 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 ☑ No

If yes, NDA #_____ Drug Name _____

If the answer to Questions 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: <u>FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES</u>
(Answer either #1 or #2, as appropriate)

1. <u>Single active ingredient product</u>.

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) coontaining 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 # 20-945 norvir (ritonavir) capsules gel + gelatin
NDA # 20-659 norvir (ritonavir) oral solution
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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 # 863

Investigation #2, Study # 720

Investigation #3, Study # 765

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. 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 # _ [redacted] ☑ Yes ☐ No

If no, explain: _____

_____

Investigation #2, IND # _ [redacted] ☑ Yes ☐ No

If 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, IND # _____

If yes or no, explain: _____

_____

Investigation #2, IND # _____

If yes or 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: _____

_____

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ON ORIGINAL

/S/ 9-15-00
Signature of Preparer Date
Title: Regulatory Management Officer

/S/ for HJ 9/20/00
Signature of Office or Division Director Date

Please see next page.

cc:
Archival NDA
HFD-xxx/Division File
HFD-xxx/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS./T.Crescenzi

Addendum:

Although this product does not fit the regulatory definition of a new chemical entity [21 CFR 314.108(a)], we recommend that it be considered for 5 years of exclusivity. The principal active ingredient (lopinavir) has not been previously approved. Ritonavir, which has been previously approved, is present only for the purpose of inhibiting the metabolism of lopinavir, thus increasing its plasma levels. Ritonavir is not present at pharmacologically active levels.

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
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100 Abbott Park Road
Abbott Park, Illinois 60064-6108

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

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.

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

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	021226	**Trade Name:**	LOPINAVIR/RITONAVIR 133.3/33.3 CAPSULE
Supplement Number:	000	**Generic Name:**	LOPINAVIR/RITONAVIR 133.3/33.3 CAPSULE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF HIV INFECTION
Action Date:	6/1/00		

Indication # 1 Treatment of HIV-1

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NEW FORMULATION developed with this submission

Comments (if any):

Lower Range	Upper Range	Status	Date
6 months	12 years	Deferred	6/1/03

Comments: Studies from birth to 6 months are currently being designed

This page was last edited on 9/8/00

/S/

Signature

9-8-00

Date

Executive Summary

This executive summary contains the Recommendations and the Summary of Clinical Findings for NDA 21-226, KALETRA (lopinavir/ritonavir), previously called ABT-378/ritonavir, for the treatment of HIV infection. In this review, the terms KALETRA and ABT-378/ritonavir will be used interchangeably.

I. Recommendations

A. Recommendation

Based on the data submitted by Abbott Laboratories in support of accelerated approval of KALETRA for the treatment of HIV infection, it is recommended that this application receive an approval action. The information contained in this application fulfils the intent of the accelerated approval regulations. The results from 5 clinical trials in adults and the expanded access program clearly demonstrate a favorable safety and efficacy profile for both treatment naïve and treatment experienced patients.

B. Recommended Phase 4 studies or marketing restrictions

1. Accelerated Approval Commitments

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

2. Phase 4 Commitments:

In addition to the accelerated approval commitments (listed above), the applicant has agreed to the following phase IV commitments: (a) completion and submission of preclinical carcinogenicity studies; (b) submission of additional stability information on the capsule and solution, and reassessment of related specifications; (c) further *in vitro* and *in vivo* investigation of the resistance and cross-resistance profiles; (d) development of appropriate dosing recommendations for administration in patients with hepatic impairment, and coadministration with other protease inhibitors (PIs), rifampin, and efavirenz or

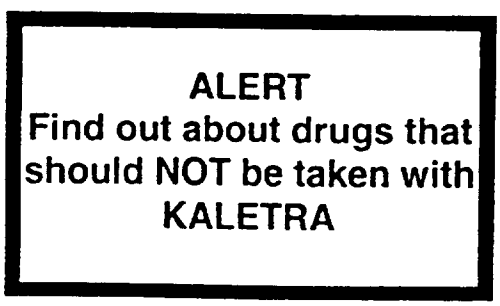
nevirapine; (e) investigation of the CYP2D6 inhibitory potential; (f) evaluation of pK/pD relationships; (g) investigation of once-daily administration, and higher dose administration; (h) investigation of suspected PI-associated class adverse events: fat redistribution and fracture development; and (i) development of an educational program for providers and patients re: avoidance of drug interactions. The reader should refer to the approval letter for further details on phase 4 commitments.

C. Risk Communication to Patients and Healthcare professionals

Described below is a risk communication strategy aimed at reducing the occurrence of serious and life-threatening drug interactions. This strategy is designed to alert patients and pharmacists about drugs that are contraindicated or drugs that should not be coadministered with KALETRA. This plan is not unique to KALETRA; all sponsors of antiretrovirals with drug interactions listed in the CONTRAINDCATIONS section will be notified of this plan.

We recognize that the agency has several mechanisms such as a MediGuide or patient package insert (PPI) to inform patients about particular contraindications and warnings for a given product. Although the MediGuide and PPI are good ways to communicate risks to patients, these mechanisms rely on a health care professional to provide these materials to patients with every prescription. We recognize that this information is not always provided to patients, or if provided, patients may not have this information readily available when taking a newly prescribed medication. In addition, multiple healthcare providers and pharmacies are involved in the prescribing and dispensing of medications to HIV-infected patients. Given these variables, the potential for serious and life-threatening drug interactions will exist.

Therefore we tried to develop a mechanism by which patients could be frequently and easily reminded of the potential for drug interactions. We believe that an "Alert" message directed for patients and displayed on a product's bottle could serve as a potentially important risk communication to reduce drug interactions. We hope that patients will see this alert each time they take a dose of KALETRA and contact a health care provider prior to taking a newly prescribed medication. Included below is a mock-up of proposed labeling that would be placed on bottles at the time of manufacturing/labeling. The box and lettering is in red for ease of recognition.



The applicant has agreed to incorporate this "Alert" on the product's bottle labeling at the time of product launch. In addition, a statement on the bottle that states, "Note to Pharmacist: Do not cover ALERT box with pharmacy label," is also included on the bottle.

In addition, references to the product alert are mentioned in the WARNINGS and PRECAUTIONS section of the package insert and t and patient package insert.

We feel that this plan may be able to reduce the potential for serious and life-threatening drug interactions. The division will explore mechanisms with OPDRA to evaluate the impact of this Alert box.

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II. Summary of clinical findings

A. Overview of clinical program

Trade name: KALETRA
Formulation: 133/33 mg capsules
Dosage: 400/100 mg BID

Proposed indication: KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV infection

The studies forming the basis of approval are briefly summarized in the table below.

Overview of Clinical Trials Submitted in NDA

Study Number	Patient Population (N)	ABT-378/ritonavir doses and control arms	Design
Phase 2			
M97-720	Naïve (N=100)	200/100 + d4T + 3TC 400/100 + d4T + 3TC 400/200 + d4T + 3TC	Randomized, Open-Label, Dose Ranging
M97-765	Experienced (N=70)	400/100 + NVP +RTIs 400/200 + NVP +RTIs	Blinded, Randomized, Dose Ranging
M98-957	Experienced (N=57)	400/100 + EFV +RTIs 533/133 + EFV +RTIs	Randomized, Open-label
Phase 3			
M98-863	Naïve (N=686)	400/100 + d4T + 3TC Nelfinavir + d4T + 3TC	Randomized, Double-Blind
M98-888	Experienced (N=300) Interim results on 118	400/100 + NVP + RTIs PI Choice + NVP + RTIs	Randomized, Open-label

B. Efficacy

The clinical activity of ABT-378/ritonavir has been demonstrated in both treatment naïve and treatment experienced patients. At the time of accelerated approval for other antiretroviral drugs, determination of efficacy was often based on studies conducted in treatment naïve patients. For this NDA, the applicant undertook a development program that evaluated ABT-378/ritonavir in several different patient populations, including treatment naïve, first PI failures and multiple PI-experienced patients.

At 24 weeks, a greater proportion of patients randomized to ABT-378/ritonavir, as compared to those randomized to nelfinavir, had HIV RNA < 400 copies/mL. Notably, response rates for ABT-378/ritonavir were similar across subgroups (baseline HIV RNA > 100,000 copies/mL and CD4 < 50 cells) whereas for nelfinavir the 24 week virologic response was lower for subgroups with higher baseline HIV RNA or lower baseline CD4 counts. These results suggest that ABT-378/ritonavir may be a preferred treatment for antiretroviral naïve patients, particularly those with high baseline HIV RNA levels and/or low CD4 cell counts.

The applicant has demonstrated that ABT-378/ritonavir has antiviral activity in patients who have previously received one PI containing regimen and in patients who had previously received multiple PIs. Historically, virologic response rates for antiretroviral experienced patients have typically been lower than that for treatment naïve patients. In this application the overall 24-week virologic response rate (HIV RNA < 400 copies/mL) in an analysis of pooled data from two phase 2 trials in PI experienced patients (study #756, and #957) was 73.6%. This was somewhat lower than that observed in trials enrolling naive patients (studies #720 and #863) in which the overall response rate was 80.6%. However, virologic response rates in studies of PI experienced patients receiving ABT-378/ritonavir appear to be greater than that seen in other trials with similar patient populations. In addition, an interim analysis of an ongoing, randomized, phase 3 study (#888) in which ABT-378/ritonavir is being compared to marketed protease inhibitors (investigator's choice of one or two) showed a virologic response rate for those randomized to ABT-378/ritonavir of 73%. This is quite similar to the results of the two phase 2 trials in PI experienced patients. In addition, the response rate in this interim look is higher than that of the control arm.

It will be important to determine if the response rates observed in the phase 3 program are sustained over 48+ weeks. Studies 863 and 888 will be submitted to the division in support of traditional approval at a later time.

C. Safety

1. Adequacy of safety testing:

Five hundred and twenty nine patients received ABT-378/ritonavir at the to be marketed dose (400/100 mg BID) for 24 – 72 weeks in the phase 2 and 3 program. In addition, ABT-378/ritonavir was administered to over 3,000 patients with limited treatment options in an expanded access program. This program provides supplemental safety data. Patients were followed for adverse events and laboratory abnormalities every 4 weeks for the first 24 weeks then every 8 weeks thereafter.

Both the size of the safety data base and the adequacy of patient monitoring and follow up is consistent with that of other antiretroviral agents that have been granted accelerated approval.

2. Common Adverse Events and Laboratory Abnormalities

The tolerability of ABT-378/ritonavir was similar to that of nelfinavir in a phase 3 study. The most common adverse events and laboratory abnormalities associated with ABT-378/ritonavir are GI intolerance (nausea, diarrhea), transaminase elevations and lipid abnormalities. Evidence of these events was observed in preclinical studies in rats and dogs.

Clinical Events:

Diarrhea was the most common adverse event and occurred in approximately 15% of all patients who received ABT-378/ritonavir at 400/100 or 533/133 mg BID. Other events such as nausea, asthenia, headache and abdominal pain occurred in approximately 5%. ABT-378/ritonavir is better tolerated than ritonavir at standard doses (600 mg BID). The incidence of adverse events was similar between naïve and experienced patients, however more naïve patients experienced nausea compared to experienced patients.

Selected Laboratory Abnormalities:

Transaminase elevations occurred in approximately 2.5% of patients enrolled in the phase 2 and 3 trials. The incidence was similar in both naïve and experienced patients. However, the frequency of these abnormalities was higer in phase 2 trials than in the larger phase 3 study (#863). At present this cannot be explained. Of interest, few patients permanently discontinued ABT-378/ritonavir treatment for transaminase abnormalities and no patient developed concomitant grade 3+ elevations in ALT and bilirubin. Patients with hepatitis B or C had an increased risk of transaminase elevations. However these patients were usually clinically asymptomatic and were able to continue treatment with ABT-378/ritonavir.

A statement is included in the package insert regarding use of ABT-378/ritonavir in patients with underlying hepatic impairment such as hepatitis B or C.

Overall, in an integrated safety analysis, approximately 9% of patients receiving ABT-378/ritonavir developed cholesterol > 300 mg/dL, 11% developed triglycerides > 750 mg/dL and 2.6% of patients developed triglycerides > 1500 mg/dL. The frequency of lipid abnormalities appeared to be increased among patients with previous antiretroviral experience compared to those patients who were antiretroviral naïve. There was a 2.5 fold increase in the proportion of antiretroviral experienced patients who developed cholesterol > 300 mg/dL and a 5 fold increase in the proportion of experienced patients who developed triglycerides > 750 mg/dL compared to antiretroviral naïve patients. This may in part be due to advanced HIV disease and/or prior PI treatment.

Hypertriglyceridemia is a known risk factor for the development of pancreatitis. The magnitude of elevations necessary to increase the risk is not precisely known; however, some sources states that levels exceeding 1000 mg/dL may put individuals at increased risk. Since some patients with KALETRA have had marked elevations in triglycerides, pancreatitis is a potential risk. To date, the frequency of pancreatitis in phase 2 and 3 trials and the expanded access program is less than 1%, which is similar to the frequency reported in HIV infected patients receiving combination antiretroviral therapy. Four patients in the KALETRA safety database reported hypertriglyceridemia at the time of the event.

A statement in the Warning section of the package insert was included to alert physicians and patients that pancreatitis has been observed, including those with marked triglyceride elevations.

3. Drug-drug interaction potential

Both lopinavir and ritonavir are extensively metabolized by the hepatic cytochrome P450 system, and almost exclusively by the CYP3A isozyme. Ritonavir is a potent inhibitor of CYP3A. Therefore, KALETRA has the potential to interact with many CYP3A inhibitors, inducers and substrates. In addition ritonavir is known to inhibit CYP2D6 although to a lesser degree than CYP3A4.

Drugs that are contraindicated and not recommended for coadministration with KALETRA are predominately displayed in table format in the Contraindication and Precaution sections of the package insert. Statements are also included in the Warning section and also referenced in the tables in the precaution section, when appropriate. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

The applicant has implemented a risk communication mechanism, suggested by this division, in an attempt to reduce potentially serious and/or life threatening drug interactions. Please refer to section I.C. Risk Communication to Patients and Healthcare professionals for details. In addition, the applicant has an

ongoing commitment to develop educational materials for patients and healthcare workers regarding avoidance of drug interactions

4. Effect of trial exclusions on safety profile vs expected marketed population

Patients with grade 3+ transaminase elevations at baseline were excluded from the trials. Based on phase 2 study data, in which patients with baseline transaminase abnormalities or hepatitis B and C were at risk for development of increasing transaminases, caution should be used when administering KALETRA in these patients. In addition, as a phase 4 commitment, the applicant has agreed to conduct a pharmacokinetic study in patients with mild and moderate hepatic dysfunction to determine whether dosage adjustments are needed and to explore safety in patients with hepatic dysfunction.

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5. Recommended Warnings

Warnings regarding the potential for drug interactions, in particular sildenafil, lovastatin, simvastatin and St. John's wort are included. In addition a warning regarding the development of new onset diabetes, exacerbation of pre-existing diabetes mellitus, and hyperglycemia, which are class labeling for the HIV PIs are displayed in the package insert. Risk of pancreatitis and monitoring recommendations are also included.

6. Safety of KALETRA in relation to other PIs.

The safety profile of KALETRA has been compared to nelfinavir in study 863 and investigator selected PI regimens (ISPIs) in study 888. Regimens appeared to be similarly tolerated. More patients receiving KALETRA experienced vomiting, taste perversion and increases in lipid levels compared to patients receiving nelfinavir. In study 888, grade 3+ laboratory abnormalities occurred with similar frequency between treatment groups, however more patients receiving ISPI(s) experienced asthenia and anorexia.

7. Unresolved safety issues

Increases in lipids and transaminases, and gastrointestinal intolerance associated with KALETRA have been well characterized. However, the risk of pancreatitis in patients receiving KALETRA, particularly those with elevations of triglycerides, needs to be further characterized in ongoing studies. In addition, the long term consequences of metabolic complications secondary to antiretroviral therapies are being investigated in multiple studies including those sponsored by a collaborative group of antiretroviral sponsors. The applicant is collecting longer-term safety data to determine if any new safety concerns arise with continued dosing of KALETRA.

D. Choice of Dosing Regimen: Dose-toxicity and dose-response relationships

The proposed marketing dose of KALETRA capsules is 400/100 mg BID. Each KALETRA capsule is a coformulation of 133 mg of ABT-378 plus 33 mg of ritonavir. At the proposed marketing dose, patients will take three capsules twice daily.

One of the objectives of the phase 1 and 2 development of ABT-378 was to maximize ABT-378 exposures, such that there would be a substantial ratio between plasma concentrations and in vitro inhibitory concentrations. The contribution of ritonavir in this fixed combination product is for pharmacologic enhancement of ABT-378 levels; it is not intended to contribute to the overall virologic efficacy. Via metabolic inhibition of CYP3A ritonavir increases ABT-378 concentrations for sustained periods allowing for less frequent dosing intervals.

Less frequent dosing intervals may contribute to overall patient compliance and therefore prolonged viral suppression. Therefore this drug product fulfills the requirements for fixed-combination prescription drugs in that the ritonavir component is a necessary component to provide adequate concentrations of lopinavir, which produces the antiviral activity.

The applicant studied a range of doses during the phase I/II program including, 200/100, 400/100 and 400/200 mg BID. The 400/100 mg BID regimen was chosen, in part, based on differences in rates of AE/laboratory abnormalities. Moderate or severe nausea and vomiting occurred at higher rates for the 400/200 mg vs the 400/100 mg dose groups in study 720. There also were also slightly higher rates of diarrhea with the 400/200 mg dose. There appeared to be a greater risk for marked lipid elevations with the 400/200 mg dose. In addition dose selection was based on the ability to maintain robust plasma concentrations/EC_{50} values throughout the dosing interval. Mean C_{min} values for ABT-378/ritonavir 200/100 mg BID, 400/100 mg BID and 400/200 mg BID exceeded the protein binding –corrected EC_{50} for wild type HIV by 50, 70 and 100 fold, respectively. Therefore, the applicant chose 400/100 mg as the best tolerated dose with the highest "inhibitory ratio". They predicted that this dose would allow improved antiviral coverage for a spectrum of HIV infected patients including those harboring strains with reduced phenotypic susceptibility. Overall the dosing regimen of 400/100 mg BID is reasonable with respect to pharmacokinetics, safety and efficacy. However, it should be emphasized that it is difficult to determine an exact inhibitory quotient or ratio due to variability in measurements of patient plasma concentrations and due to the many possible methods that can be used for determining an in vitro EC_{50}.

1. Dose modification recommendations

A dose increase of ABT-378/ritonavir to 533/133 mg BID when coadministered with efavirenz or nevirapine should be considered for treatment experienced patients for which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Consideration for this dose increase is based on the following information.

- Pharmacokinetic results from several drug interaction studies/substudies in healthy volunteers and HIV infected adults given efavirenz and pediatric patients given nevirapine showed a reduction in ABT-378 concentrations by approximately 30%.
- Numerically higher response rates (not statistically significant) in patients receiving 533/133 mg dose compared to the 400/100 mg dose in study 957.

However, a dose increase may not be necessary for patients who have previously received one protease inhibitor and/or where reduced susceptibility is not suspected. This is supported by the results from study 765 in that similar

response rates where noted for patients receiving 400/100 mg and 400/200 mg in combination with nevirapine.

3. Unresolved dosing issues

There are no unresolved dosing issues at this time; however, the applicant should determine if dose adjustments are needed in patients with hepatic impairment. In addition, the applicant is currently pursuing once daily administration and exploring treatment with higher doses of KALTERA for multi-drug resistant patients.

E. Special Populations

1. Gender analyses

The applicant conducted analyses by gender, race, and age. No statistically significant differences in the proportion of patients with HIV RNA < 400 copies/mL were noted by race. Also no consistent trends were seen between subgroups defined by gender or race.

No statistically significant differences in mean CD4 cell counts were observed between patients in subgroups defined by gender, age or race.

The applicant also reported that the safety profile of KALETRA did not differ according to age, sex or racial characteristics.

2. Other special populations

a. Elderly

Clinical studies of KALETRA did not include sufficient numbers of subject's aged 65 and over to determine whether they respond differently from younger subjects.

b. Renal and Hepatic impairment

It is unlikely that ABT-378/ritonavir will be affected in patients with renal impairment or by hemodialysis. However ABT-378/ritonavir may be affected in patients with hepatic impairment. For a phase 4 commitment the applicant will be requested to conduct a study in patients with mild and moderate hepatic impairment in order to determine dosing recommendations for this patient population. In addition, a statement has been included in the Precautions section of the package insert regarding use of ABT-378/ritonavir in patients with hepatic impairment.

3. Status of pediatric studies

The applicant was asked to conduct multiple-dose pharmacokinetic, safety and activity study(ies) of ABT-378/ritonavir in combination with other antiretroviral agents in HIV-infected pediatric patients and multiple-dose pharmacokinetic and safety study(ies) of ABT-378 in HIV-exposed neonates born to HIV-infected mothers. HIV-infected pediatric patients from 1 month to 16 years and HIV-exposed neonates (born to HIV-infected mothers) were to be enrolled.

Abbott has completed a multi-dose pharmacokinetic, safety and activity study in 100 pediatric patients aged 6 months to 12 years. The applicant has also agreed to conduct a multi-dose pharmacokinetic and safety study in HIV-exposed neonates. The latter study is in the planning stages and has not been initiated to date. Please refer to Dr. Linda Lewis' review for further details regarding the activity of KALETRA in pediatric patients. Patients aged 13 years and older were permitted to enroll in the adult trials.

/S/

Kimberly A. Struble, PharmD
Regulatory Review Officer

Concurrence:
HFD-530/MOTL/Murray /S/ 10/24/00
HFD-530/DivDir/Jolson /S/ 10/23/00

cc:
Original NDA 21-226
Division File
HFD-530/RRO/Struble
HFD-530/MO/Murray
HFD-530/CSO/Lynche
HFD-530/Stat/Soon
HFD-530/Biopharm/Reynolds, Kim
HFD-530/Chem/Miller, Lo
HFD-530/Pharm/Tox/Farrelly, Zhang

Group Leader's Memorandum

NDA 21-226, KALETRA (lopinavir/ritonavir) capsules
NDA 21-251, KALETRA (lopinavir/ritonavir) oral suspension

Background
Abbott Laboratories submitted two new drug applications for the new molecular entity lopinavir, an HIV protease inhibitor (PI) co-formulated in a 4:1 ratio with ritonavir, the applicant's currently marketed PI. NDA 21-226 was submitted in support of the capsule formulation and NDA 21-251 was submitted in support of an oral suspension intended primarily for pediatric use. The proposed marketing doses for the capsule formulation is 400/100 mg BID and for the oral suspension in children 6 mos to 12 years of age is 10-12 mg/kg BID (depending on body weight). In the application, Abbott has diligently addressed the applicable regulatory requirements including, safety, efficacy, financial disclosure, gender and pediatric issues, and fixed drug combination issues.

Dose Selection
The applicant has satisfied regulations pertaining to fixed drug combinations (§CFR 300.50) in that they have conclusively demonstrated in both preclinical and early clinical development that both drugs are necessary for the effectiveness of the combination. In this combination regimen, ritonavir is used at a virologically subtherapeutic dose (plasma concentrations of ritonavir are only 7% of that of the approved dose of 600 mg bid) solely to increase lopinavir concentrations via inhibition of CYP3A metabolism. Based on achievable concentration ratios and in vitro susceptibility of HIV to lopinavir and ritonavir, Abbott has estimated that lopinavir is responsible for nearly all of the observed antiviral activity.

In the presence of "low" doses of ritonavir, lopinavir concentrations are increased greater than 100-fold. Given this profound pharmacologic interaction, Abbott has sought to improve upon previously available PI by attempting to provide a larger margin between minimal plasma concentrations and the predicted susceptibility of the virus based on in vitro inhibitory concentrations corrected for protein binding. Abbott also predicted that the ability to achieve robust concentrations of KALETRA might also enable the treatment of HIV strains with reduced susceptibility.

Therefore the development plan sought to define a dose of KALETRA that would allow a margin of error in dosing while maintaining an acceptable level of toxicity. Providing robust concentrations is hoped to correct for delayed or missed doses, variability in viral susceptibility and variability in drug metabolism. This concept breaks from previous tradition in which a minimally effective dose was sometimes selected, primarily because of limitations imposed by poor bioavailability or poor tolerability at higher doses. Throughout the phase 2 and 3 development program, several doses of lopinavir ritonavir were evaluated including 200/100 mg BID,

400/100 mg BID, 400/200 mg BID and 533/133 mg BID. All doses appeared to have comparable virologic efficacy and tolerability in treatment naïve patients. A dose of 400/100-mg BID was chosen to target robust concentrations with the intention of providing sufficient coverage for the wide variability of patient characteristics (e.g., metabolic clearance) and viral susceptibility that occurs in clinical practice. The product label will state that a dose increase to 533/133 mg bid should be considered for concomitant use with efavirenz or nevirapine (drugs which decrease plasma concentrations of lopinavir by approximately 30%), in patients in which reduced susceptibility to lopinavir is suspected (by treatment history or laboratory evidence).

Efficacy

The efficacy of ABT-378 has been demonstrated in phase 2 and 3 clinical studies in adults and children with varying degrees of antiretroviral experience. To date, patients receiving regimens including KALETRA in phase 2 and 3 studies have had favorable rates of virologic response particularly when considering treatment histories of participants. In the double-blind, randomized, phase 3 study of treatment naïve patients (study #863), KALETRA plus two nucleoside reverse transcriptase inhibitors (NRTI) yielded a larger percentage of treatment successes than nelfinavir plus 2 NRTI at 24 weeks (79% vs 71%, respectively had plasma HIV RNA levels < 400 copies/mL). This difference was statistically significant. Importantly, the difference in response rates widened between the two treatment groups, in favor of the KALETRA group, for patients with baseline HIV-RNA levels exceeding 100,000 copies/mL.

In an uncontrolled, dose-ranging, phase 2 study (#765) patients with previous exposure to a first PI-containing regimen received one of two doses of KALETRA in combination with nevirapine and at least one new NRTI. Approximately two-thirds of patients receiving both dosing regimens were virologic responders (< 400 copies/mL, intent to treat analysis) at 48 weeks. Such a response is roughly comparable to that reported for other studies of first PI regimens in naïve patients. In addition, in an interim analysis of a randomized phase 3 study of KALETRA vs one or two marketed PI (per physician's choice), both combined with nevirapine and NRTIs, the KALETRA containing arm had numerically higher virologic response rates (< 400 copies/mL) at 16 and 24 weeks than the physician's choice arm. However, it should be cautioned that the latter are preliminary data from a study that has only recently completed enrollment.

In another dose-ranging phase 2 study in multiple PI experienced but NNRTI naive patients, KALETRA at one of two doses was administered with efavirenz and NRTIs. Two doses of KALETRA were studied since efavirenz was known to decrease lopinavir concentrations by approximately 30%. Twenty-four week virologic success rates (< 400 copies) were observed in about two thirds of the patients receiving KALETRA 400/100 mg with somewhat higher response rates (but not statistically significant) for those receiving KALETRA 533/133 mg. In a retrospective analysis of virologic success at 24 weeks according to baseline

resistance measurements, virologic success rates were lower for those patients harboring isolates demonstrating reduced phenotypic susceptibility to lopinavir compared to viruses with wild type susceptibility. Also reduced response rates were observed for those patients with greater numbers of primary and secondary PI mutations (selected by the marketed PI) compared to those with lesser numbers of mutations. The retrospective analyses showing a trend between baseline susceptibility and virologic response supports the fact that lopinavir is an active antiretroviral and also demonstrates that an accumulation of mutations selected by marketed PI will ultimately limit the response to a KALETRA containing regimen.

Abbott also evaluated the efficacy of KALETRA in 100 pediatric patients ages 6 months and above. KALETRA was administered with 2 NRTI in treatment naïve patients and in combination with nevirapine and NRTIs in treatment experienced patients. Virologic successes at 24 weeks were roughly comparable with those seen in adults with comparable treatment experience. Treatment experienced pediatric patients had a numerically lower response rate than treatment naïve patients.

Safety

Clinical

Five hundred and twenty nine patients received KALETRA at the to be marketed dose (400/100 mg BID) for 24 – 72 weeks in the phase 2 and 3 program. In addition, KALETRA was administered to more than 3,000 patients with limited treatrnent options in an ongoing expanded access program. In summary, KALETRA did not appear to be associated with any new toxicities that have not already been reported with use of ritonavir. Most of the clinical and laboratory adverse events reported for KALETRA appear to be related to the ritonavir component of the drug product; however, KALETRA was much better tolerated than the approved dose of ritonavir. The most common clinical adverse events observed in clinical studies were gastrointestinal consisting mostly of diarrhea and nausea. Fatigue and headache were also observed. Generally, these more common adverse events were not dose limiting; approximately 3% of patients in clinical trials discontinued medications secondary to adverse events. The safety profile in children was similar to that observed in adults.

An adverse event of potential concern is pancreatitis, which will be described in the Warning section of the KALETRA label. Overall pancreatitis occurred in approximately 1% of individuals receiving KALETRA in clinical trials and expanded access. The frequency is less than that historically associated with didanosine administration and about equal to the frequency seen in other trials of combination antiretrovirals. Although the frequency of pancreatitis among patients receiving KALETRA did not signal a particularly strong association, there was one reported case of pancreatitis in the pediatric study demonstrating a possible positive rechallenge. In addition, since hypertriglyceridemia has been associated with the development of pancreatitis and KALETRA produces

increases in triglycerides, the potential for pancreatitis is a concern. Among the pancreatitis cases reported in the clinical trials, pancreatitis was observed with and without concomitant triglyceride elevations.

Manifestations of fat redistribution was observed in several patients receiving KALETRA. However, since there is no accepted case definition, and since long term follow-up has not been completed in a large number of patients, it was not possible to define causal relationships or further characterize the frequency or time course for the development of this syndrome.

Laboratory

As was observed with ritonavir at 600 mg bid, increases in triglycerides and cholesterol were observed in patients receiving KALETRA, although perhaps to a lesser degree. However some patients did develop extreme elevations in triglycerides and cholesterol while receiving KALETRA. These laboratories will need to be monitored and treated appropriately as will be stated in the product label.

Transaminase elevations were observed in phase 2 and 3 studies. In the phase 3 study comparing KALETRA to nelfinavir in treatment naïve patients, the frequency of such abnormalities was similar and relatively infrequent (1% and 2.5% of patients receiving KALETRA and nelfinavir, respectively, had an increase in ALT greater than 5 times the upper limit of normal). A larger percentage of patients had transaminase elevations among those participating in phase 2 studies, however. Patients with baseline abnormalities and patients chronically infected with hepatitis B or C appeared to be at increased risk. In many cases drug was continued despite elevations in enzymes without adverse clinical consequences or laboratory evidence of hepatic decline.

Drug Interactions

In that the drug product KALETRA contains ritonavir to specifically inhibit the metabolism of lopinavir, interactions with other drugs similarly metabolized is expected. As for other drugs in the protease inhibitor class, several drugs (primarily those metabolized by CYP3A) are contraindicated for use with KALETRA. In addition, some drugs should not be used with KALETRA since they may decrease lopinavir levels which could result in loss of efficacy.

Recommendations

I fully concur with the clinical review prepared by Kimberly Struble PharmD. As stated in her review, the applicant has clearly demonstrated that KALETRA at the proposed doses for marketing is a safe and effective drug for the treatment of HIV infection when combined with other antiretrovirals. KALETRA has demonstrated robust activity in treatment naïve individuals, pediatric patients, and patients failing a first regimen containing a PI. In addition, KALETRA combined with efavirenz appeared to be active in a sizeable proportion of NNRTI naïve patients who had previously received multiple PI. Its apparent therapeutic

advantages with respect to efficacy, ease of dosing, and tolerability fulfills the intent of accelerated approval regulations in that this drug has both therapeutic advantages over existing treatments and may be able to treat patients who have failed other options.

/S/ 9/12/00

Jeffrey S. Murray
Medical Team Leader

Division Director Memorandum

NDA:	**21-226 (capsules)** **21-251 (solution)**
Drug and indication:	**Lopinavir/Ritonavir (Kaletra)**
Dose:	**Adult - 400 mg/100 mg b.i.d.** **Pediatric - 10-12 mg/kg b.i.d. based on lopinavir component and body weight, up to adult dose**
Applicant:	**Abbott Laboratories**
Submission dated:	**June 1, 2000**
Date of Memorandum:	**September 15, 2000**

In these applications, the sponsor has requested approval for lopinavir/ritonavir capsules and solution for the treatment of HIV in combination with other antiretroviral agents in adults and pediatric patients age six months and older. In support of this request, the sponsor has submitted reports of five ongoing, controlled trials being conducted in 1031 adults, one trial being conducted in 100 pediatric patients, and uncontrolled safety data from an early access program in 3380 individuals. The studied adult patient population includes treatment naive individuals (Studies 720 and 863), patients enrolling following a first protease inhibitor (PI) regimen failure (Studies 765 and 888, preliminarily), and patients previously treated with two or more PI-based regimens (Study 957). The pediatric study includes treatment naive and experienced children ranging in age from 6 months to 12 years. In the submitted database, the duration of treatment experience ranges from 24 to 72 weeks in the controlled trials, and from less than 1 month to 8.7 months (mean 2.3 months) in the early access program.

I am in concurrence with the consensus of the review team that these applications are approvable. The data submitted in support of these applications demonstrate that treatment with lopinavir/ritonavir has a favorable risk to benefit ratio and is likely to be associated with clinical benefit in patients for whom antiretroviral therapy is recommended.

The following issues pertaining to this regulatory action merit comment:

1. Provisions of accelerated approval

These applications are being approved under the provisions for accelerated approval (21 CFR 314.500, Subpart H). In accordance with this regulation, the submitted data provide evidence that treatment with lopinavir/ritonavir provides a meaningful therapeutic benefit to patients over existing treatments. This claim is supported by the results of trials conducted in treatment-experienced adult and pediatric patients (Studies 765, 957, 888 preliminarily, and 940) in which the ability to treat patients unresponsive to, or intolerant of, previous antiretroviral therapy, was

evaluated. Results from these studies suggest that lopinavir/ritonavir may be useful in this population, however this issue will be more extensively addressed in the ongoing phase III trial that will be submitted to support traditional approval. The submitted data additionally support the potential therapeutic advantages of lopinavir/ritonavir in treatment naive individuals as demonstrated by acceptable tolerability and robust antiviral activity in this population. Therefore, this development program satisfies the intent of the accelerated approval provisions; the adequacy of plans for traditional approval are discussed below.

2. Rationale for dose and fixed combination

Lopinavir/ritonavir is the first coformulated dual protease inhibitor to be approved. However, the use of dual protease inhibitor therapy, including the use of low-dose ritonavir to boost the plasma concentration of the second protease inhibitor, has become increasingly common in clinical practice.

Among the three initial doses studied (mg lopinavir/mg ritonavir = 200/100, 400/100, and 400/200), the 400/100 bid lopinavir/ritonavir dose was chosen based on the observation of higher rates of toxicity with the 400/200 vs. 400/100 regimen, and the intent to maximize trough concentrations (when 200/100 and 400/100 were compared) relative to the EC_{50}. A fourth dose (533/133) has been studied in treatment-experienced individuals receiving concomitant efavirenz. Based on the finding of numerically higher rates of viral response in patients receiving the 533/133 dose compared to the 400/100 dose and relevant pharmacokinetic data in adults and children, the label will recommend that the higher dose be considered for treatment experienced patients on concomitant efavirenz or nevirapine where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). However, further study of optimal dosing for coadministration with efavirenz or nevirapine is needed, as discussed below, under Dosing Recommendations for Concomitant Antiretrovirals.

The applicant has provided adequate evidence to satisfy the conditions of the combination drug policy, 21 CFR 300.50. Specifically, the applicant has demonstrated the contribution of each component to the claimed effect by the observations that: (a) when dosed alone, lopinavir is poorly absorbed; (b) the dose of ritonavir (100 mg), results in subtherapeutic concentrations of ritonavir (approximately 7% when compared to the approved, twice daily effective dose of 600 mg); (c) when coadministered, the plasma concentration of lopinavir is substantially increased, via metabolic inhibition by ritonavir; and (d) when coadministered, the combination product has an improved safety profile (when compared to historical data with higher doses of ritonavir), and appears to be at least as effective as its comparitors. Therefore, this product satisfies the special case (1) of the general rule in that the role of ritonavir is to enhance the effectiveness of the principal active component (lopinavir).

3. Demonstration of efficacy

As detailed in the clinical reviews, five trials in adults, and one trial in children, provide evidence to support the efficacy of lopinavir/ritonavir for treatment of HIV in naive and treatment experienced individuals.

Treatment-naive individuals: In the largest trial (Study 863), conducted in 686 treatment-naive adults, the effectiveness of a combination regimen with lopinavir/ritonavir in suppressing virus through 24 weeks of treatment was demonstrated. After 24 weeks of treatment, 79%* (65%) of patients randomized to the lopinavir/ritonavir regimen had a viral load <400 (<50) copies/mL compared to 71% (60%) in the nelfinavir-treatment group (*$p<0.05$). Generally similar rates of viral suppression were demonstrated in lopinavir/ritonavir-treated patients regardless of baseline viral load or CD4 cell count stratum. The potential durability of a lopinavir/ritonavir based regimen in naive individuals was investigated in the original dose-finding study (Study 720). In this smaller study, among subjects who received the to-be-marketed dose, 41/51 (80%) of patients had HIV RNA < 400 copies/mL through 72 weeks of treatment. Together these studies suggest that therapy with lopinavir/ritonavir is likely to provide a high likelihood, and an encouraging durability, of virologic response.

Treatment-experienced individuals: The potential utility of lopinavir/ritonavir in treatment experienced individuals is suggested by the promising results of phase II studies conducted in patients with virologic failure after a first PI-containing regimen (Study 765), or multiple regimens (Study 957), and by the preliminary results of the applicant's phase III study (888).

In Study 765, 73% of patients who received lopinavir/ritonavir in combination with nevirapine had viral suppression through 72 weeks of treatment. While this study design does not allow for the determination of the independent contribution of lopinavir/ritonavir (due to the addition of nevirapine after two weeks), the high rate and durability of response suggest that lopinavir/ritonavir is actively contributing to the effectiveness of the four-component regimen. This observation is further supported by the preliminary results of Study 888 (after 118/300 patients had been enrolled) in which the lopinavir-ritonavir treatment group had at least comparable rates of response compared to investigator-chosen PI-regimens.

The results of Study 957, and in particular, the observation of a dose-response between 400/100 and 533/133 groups after 16 weeks of treatment, lend further support for the utility of lopinavir/ritonavir in treatment experienced individuals.

4. Considerations for safety

The safety of lopinavir/ritonavir has been evaluated at the to be marketed dose in 529 individuals in controlled trials (duration 24 to 72 weeks of treatment), and in 3380 additional patients who received at least one dose in an early access program. The tolerability of the combination is generally acceptable with the more frequent adverse experiences including diarrhea, nausea and vomiting, and headache. More serious safety concerns are raised by the findings of lipid abnormalities (grade 3 or 4 cholesterol and triglyceride elevations in approximately 10% of recipients), symptoms of fat redistribution (reported in several individuals in each study), and elevations in liver transaminases (elevations > 5X ULN in approximately 2% of recipients). Of additional concern, pancreatitis occurred in approximately 1% of treated patients. In general, the types of clinical and laboratory adverse experience reported with lopinavir/ritonavir treatment are consistent with the known safety profile of ritonavir, however the rates of toxicity appear to be

generally lower with the combination.

As with ritonavir and other protease inhibitors, the risk of drug interactions is a concern, and is further discussed below.

5. Safety issues due to drug interactions

The potential for unrecognized drug interactions, between lopinavir/ritonavir and concomitant therapy, raises a significant safety issue. As detailed in the biopharmaceutics and clinical reviews, lopinavir/ritonavir is an inhibitor of the P450 isoforms, CYP3A and CYP2D6. As a result, coadministration of lopinavir/ritonavir with drugs metabolized by these isoforms may result in increased plasma concentrations of the concomitant drug and corresponding toxicity.

Accordingly, concomitant administration is contraindicated with drugs that are highly dependent on these metabolic pathways and for which elevated plasma-concentrations may lead to serious or life-threatening events. Similar contraindications are already present in the labeling of all marketed protease inhibitors.

In the NDA database, one fatality resulting from co-administration of lopinavir/ritonavir and an ergot alkaloid, was reported. In this instance, the PI and the ergot were prescribed by two different providers. In an effort to minimize similar prescribing errors, the following risk communication approaches have been developed: (a) reformatting and simplifying the drug interaction information in the product labeling (including Contraindications, Warnings, Precautions and Clinical Pharmacology sections) to highlight clinically important interactions; (b) discussion of similar information in the patient package insert; and (c) development of a patient-oriented "ALERT" message applied directly to each medication bottle to reinforce the need to find out if lopinavir/ritonavir may be safety taken with a patient's other medications.

Because it is recognized that patients may receive medication from multiple physicians, as well as from over-the-counter purchasing, the container-message approach to risk communication is directed specifically to the patient. Antiretroviral products are particularly suitable to this approach because most are distributed by manufacturers in one-month unit of use containers (thus minimizing the likelihood that pharmacists will repackage them). Because lopinavir/ritonavir is not unique in its potential for significant drug interactions, DAVDP intends to request that all manufacturers of antiretrovirals with contraindicated medications provide a similar message on their product labeling.

6. Dosing recommendations with concomitant antiretrovirals

The following are additional clinically important drug interaction considerations related to concomitant antiretrovirals:

Nevirapine or efavirenz: There is conflicting data regarding the significance of the interaction between lopinavir/ritonavir and nevirapine or efavirenz. Pharmacokinetic sampling from two clinical trials (Studies 764 and 940) suggests that lopinavir concentrations are lower in the

presence of nevirapine. However, in healthy volunteers (Study 704), no interaction was suggested. In studies with efavirenz (Studies 741 and 957), lopinavir concentrations were somewhat reduced. Additionally, in clinical data from Study 957, rates of virologic response at 24 weeks were numerically but not significantly higher in the 533/133 dose group compared to the 400/100 group (82% vs. 69%, p=0.358).

Because Study 720 provides some evidence for the efficacy of the 200/100 dose in treatment naive patients, the label will recommend that a dose increase to 533/133 mg be considered for treatment experienced patients receiving concomitant nevirapine or efavirenz where reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). Further evaluation of this issue has been requested as a phase IV commitment.

Other Protease Inhibitors: As discussed in the Clinical Pharmacology review, there is limited available data to support concomitant dosing with other protease inhibitors. However, it is recognized that clinicians may wish to dose lopinavir/ritonavir concomitantly with another PI in selected treatment experienced patients and there is a need for some guidance about the expected magnitude of the interactions. Additionally, the Antiviral Drugs Advisory Committee has voiced their support for the importance of providing safety, efficacy and PK data for dual-PI use in PI labeling. Accordingly, the lopinavir/ritonavir label will provide a summary of PK results from drug interaction studies with amprenavir, indinavir and saquinavir. However, the label will also indicate the limitations of these findings, and will state that the safety and efficacy of these regimens, and their optimal dosing, have not been established.

7. Pediatric Use

The applicant has evaluated the safety and activity of lopinavir/ritonavir in 100 treatment-naive and experienced children, ages 6 months to 12 years (Study 940). The recommended pediatric weight-adjusted dose is based on the finding of comparability to adult plasma concentrations, and is further supported by safety and efficacy data from this study. As noted in the clinical review, antiviral activity was demonstrated through 24 weeks of treatment, with somewhat higher response rates noted in treatment naive children (82% vs 66%). Since nevirapine was coadministered to treatment-experienced children, the precise contribution of lopinavir/ritonavir can not be determined in this subgroup.

The safety profile of lopinavir/ritonavir appears to be similar between children and adults. However, the large amount of ethanol (42%) in the solution formulation raises an additional safety concern for children in the situation of an accidental overdose. The container label will provide a statement regarding the amount of ethanol in the solution, and the professional and patient labels will provide a warning about this concern.

There is currently no data regarding use in children younger than 6 months of age. Data on the safety and pharmacokinetics in this age group has been previously requested in a Written Request, dated March 31, 1999. Per the provisions of 21 CFR 314.55, submission of this outstanding pediatric information will be deferred until June 2003.

8. Plans for traditional approval

To fulfill the requirements of 314.500, the applicant has committed to submit the final study results of two ongoing phase III trials. These trials, being conducted in treatment naive (Study 863) and treatment experienced adults (Study 888), are expected to provide confirmatory evidence of the durability of viral suppression with lopinavir/ritonavir treatment and further data on the safety of longer-term treatment. The traditional approval plan is consistent with the division's guidance and is acceptable.

9. Phase IV commitments

In addition to the previously noted traditional approval commitments, the sponsor has agreed to the following additional phase IV commitments: (a) completion and submission of preclinical carcinogenicity studies; (b) submission of additional stability information on the capsule and solution, and reassessment of related specifications; (c) further *in vitro* and *in vivo* investigation of the resistance and cross-resistance profiles; (d) development of appropriate dosing recommendations for administration in patients with hepatic impairment, and coadministration with other PIs, rifampin, and efavirenz or nevirapine; (e) investigation of the CYP2D6 inhibitory potential; (f) evaluation of pK/pD relationships; (g) investigation of once-daily administration, and higher dose administration; (h) investigation of suspected PI-associated class adverse events: fat redistribution and fracture development; and (i) development of an educational program for providers and patients re: avoidance of drug interactions.

There are no additional outstanding regulatory issues at the time of this action. The entire team should be commended for their excellent collaborative review of these applications.

/S/

Heidi M. Jolson, M.D., M.P.H.
Director, Division of Antiviral Drug Products

cc:
NDA 21-226, 21-251
HFD-530/Struble/Murray
HFD-104/Kweder/Murphy

Team Leader Evaluation

Teamleader Evaluation of NDA 21-226

This is a drug combination of lopinavir and ritonavir called Kaletra. The sponsor (Abbott) has submitted the following studies in support of the safety of the combination:

Five nonclinical pharmacology and safety pharmacology studies,

Five acute dose toxicity studies in mice and rats,

Ten repeat dose toxicity studies in mice, rats and dogs
These include a six month study in rats and a nine month study in dogs as well as studies in neonatal and juvenile rats,

Three studies in dogs to evaluate the toxicity of added impurities,

Four reproductive toxicology studies
These include a Segment I, two Segment II and a Segment III study,

Twelve genetic toxicology studies
These include Ames, L5178/TK$^{+/-}$ mouse lymphoma, human lymphocyte in vitro cytogenetics and a mouse micronucleus assay. The studies included evaluations of various impurities.

Twenty four pharmacokinetic studies including metabolism studies.

The carcinogenicity studies to evaluate the combination are ongoing. Studies to evaluate the carcinogenicity of ritonavir have been completed and are mentioned in the label.

The combination is Pregnancy Category C, in contrast to ritonavir alone which is Pregnancy Category B. The Category C is due to deaths in the Segment III study at doses that are not maternally toxic but with poor exposure compared to the exposure in humans at the approved dose.

The only Phase 4 commitment is for the sponsor to finish and submit the results of the ongoing carcinogenicity studies.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies of KALETRA in animal systems have not been completed.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA BID). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA BID regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

Pregnancy

Pregnancy Category C. No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed **not to breast-feed if they are receiving KALETRA.**

Phase 4 commitment is to finish and submit the results of the ongoing carcinogenicity studies

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleco. ference

NDAs: **21-226 and 21-251**

Date: **September 14, 2000**

Drug: **Kaletra (lopinavir/ritonavir)**

Sponsor: **Abbott Laboratories**

BETWEEN: **Representatives of Abbott**
Eugene Sun, MD, Antiviral Venture Head
Jeanne Fox, Director, Regulatory Affairs
Rebecca Welch, Associate Director, Regulatory Affairs
Bill Monte, PhD, Special Products Division, Development
Tom Campbell, PhD, Special Products Division, Development
Efraim Shek, PhD, Pharmaceutical Products Division, Development
Ashok Katare, PhD, Pharmaceutical Products Division, Development
Soumajeet Ghosh, PhD, Pharmaceutical Products Division, Development
Howard Cheskin, PhD, Pharmaceutical Products Division, Development
John Morris, PhD, Pharmaceutical Products Division, Development

AND: **Representatives of DAVDP**
Stephen Miller, PhD, Chemistry Team Leader
Ko-yu Lo, PhD, Chemistry Reviewer
Kellie Reynolds, PharmD, Biopharmaceutics Team Leader
Kim Struble, PharmD, Regulatory Review Officer
Sylvia Lynche, PharmD, Regulatory Project Manager

Discussion: This teleconference discussed Abbott's responses (9/7/00 and 9/13/00) to FDA Chemistry requests/comments dated 9/1/00 and 9/11/00. All outstanding CMC issues were resolved. A Phase IV commitment to reassess the DS specification and DP specification was agreed by Abbott. Issues resolved are summarized as follows:

With regard to lopinavir drug substance

1. Abbott identified Lots 53-071-CA (at North Chicago), 54-309-TL, 54-312-TL and 57-412-TL (at Italy) as the first set of production scale lots manufactured with the designated production equipment. Levels of related substances seen in these lots were attributed to nominal process development. Based on this justification, FDA agreed that data from these lots should be included in the reanalysis even though their numbers/levels of impurities were substantially greater compared with the majority of the production lots.

2. DS specification -- FDA recommended to set DS specification based upon production scale lots, and a specification of 0.1% for individual impurities that have never been detected in the DS lots. Abbott reanalyzed data on 52 production scale lots and performed statistical analysis (Mean ± 3SD) on potency, moisture, and total related substances. Based on this reanalysis and existing processing ranges data, Abbott proposed the following: (i) The specification for assay (980 – 1020 ug/mg) and moisture (4.0%) remain unchanged, (ii) the specification for total related substances be revised from [redacted], and (iii) the specification for individual related substances be revised to the limit shown on page 3 of the 9/7/00 amendment. FDA found Item (i) justifiable, Item (ii) & (iii) acceptable.

3. Post Approval Stability Protocol was found acceptable.

With regard to KALETRA Capsules

4. Components/composition -- Standard amounts of each ingredient in a typical commercial scale batch was provided and

found acceptable.

5. Process-control limit (PCL) –

   (a) FDA agreed with Abbott that there will be no PCL for lopinavir since lopinavir remains unchanged on stability at all storage conditions (5°, 25° C/ [redacted] and 30° C/ [redacted]).

   (b) Ritonavir related substances (i.e., degradants [redacted] and Total) – Abbott indicated that with limit data (17 lots with 20 studies) available at the NDA filing, a "tolerance intervals" approach ($X_u = X_{ave} + 4.319$ x SD) was used to determine the "tolerance" of ritonavir degradatns. PCL = Tolerance (%) + Contribution from oleic acid (%). This model would predict with 95% confidence that 99.9% of product will test in conformance (about 1 failure in 1000). Abbott stated that for KALETRA product, it would require 40 lots to apply the Mean +3 sigma approach. Per FDA request, data from all available clinical and commercial lots (47 lots with 50 studies) were reanalyzed using the Mean + 3 sigma approach to obtain a new set of "tolerance". In addition, the contribution from oleic acid interference was able to reduce to a lower level because of having greater confidence in the analytical variability. As a result, PCLs were revised as follows: [redacted] The newly proposed PCLs are significantly lower than that proposed at the NDA filing. FDA found the new PCLs acceptable.

6. DP specification –

   (a) FDA recommended including a specification of "total degradants" for lopinavir in DP specification. Based on the upper 95% CI at 21 months at 5° C + 3 months at 25° C/ [redacted] Abbott proposed an acceptance (shelf-life) specification of " [redacted] for "Total ICH Related Substances" for lopinavir. FDA found the specification acceptable.

   (b) Acceptance limit (AL) for retonavir related substances calculated by Y=PCL +S1*T1 +S2*T2 – Calculation was performed by adding PCL + 5° C data (calculated from 12 months actual data) extrapolated to 21 months + 25° C data (calculated from 6 months primary studies at 25° C/ [redacted]) estimated at 3 months. Abbott agreed to recalculate the ALs without the RMSE term in se (Y). A new set of ALs was proposed. **ALs calculated by this approach are theoretical limits to accommodate worst case scenario.**

   (c) ALs calculated from move studies data -- FDA requested Abbott to perform statistical analysis on data from move studies. In response, linear regression analysis on data from samples stored 3 mos @ 25°C/ [redacted] (transferred from 0, 3, 6, and 9 mos at 5° C) was performed and upper 95% Confiedence Bound on the mean predicted level at 21 months at 5° C determined. **ALs calculated by this method are limits obtained from samples representing real setting.**

   Comparison of ALs by Method (b) and Method (c)

Degradant	AL by (b)	AL by (c)
[redacted]		

   The results show that ALs by the two methods are significantly different.

   In this NDA, extrapolated stability data (from 12 mons (or 9 mos from the move studies) to 24 mos) are used to determine ALs for the degradants of ritonavir. Since details of this statistical application (i.e., number of lots and number of sampling points required, best suitable statistical models etc) is not available at this time, it is difficult to know which set of ALs would be more correctly describe the product characteristics. Both FDA and Abbott agreed a looser AL by (b) should be used as the final specification. This is based on the following justification: (i) a tighter AL by (c) could run into potential compliance problem, and (ii) ALs by (b) are supported by the clinical experience with the NOVIR products. There is no safety concern for the amounts of degradants to be taken daily. Abbott agreed to reassess the DP specification when sufficient data are available (see Phase IV Commitment)

With regard to KALETRA Oral Solution

7. Reprocessing Operation -- Abbott clarified that Lot #62-328-AR-XX was manufactured to demonstrate the ability to reprocess the product. Data (9/13/00 amendment) given to support the proposed 6 months elapsed time was found acceptable.

8. Process-control limit (PCL) --

   (a) FDA agreed with Abbott that there will be no PCL for lopinavir since lopinavir remains unchanged on stability at all storage conditions (5°, 25° C [redacted] and 30° C/[redacted]).

   (b) Ritonavir related substances (i.e., degradants [redacted] and Total) -- Abbott indicated that only limited data was available for KALETRA solution (9 lots at NDA filing, and 12 lots in this amendment). Use of the Mean + 3 sigma approach can lead to a surprising increase in the risk level. Therefore, the "tolerance intervals" approach ($X_u = X_{ave} + 4.319 \times SD$) was used to determine the "tolerance" of ritonavir degradatns. PCL = Tolerance (%) + Placebo Effect (%). PCLs determined from data on 12 lots were as follows: [redacted] FDA found the proposed specification acceptable.

9. DP specification --

   (a) "Color" in Physical Examination -- Abbott agreed to add report results (Text: light yellow to orange, golden hues are encompassed by this range).

   (b) Aerobic Microbial Count -- Abbott agreed to add a limit of 100 cuf/mL.

   (c) Lopinavir ICH Total Related Substances -- Abbott proposed a shelf-Life limit of 0.5%. FDA found the specification acceptable.

   (d) Acceptance limits (AL) for ritonavir related substances calculated by Y=PCL +S1*T1 +S2*T2. Calculation was performed by adding PCL + 5° C data (calculated from 9 months actual data) extrapolated to 21 months + 25° C data (calculated from 6 months primary studies at 25° C/ [redacted] estimated at 3 months. Abbott agreed to recalculate the ALs without the RMSE term in se (Y). The new set of ALs are as follows: [redacted]. FDA found the proposed specification acceptable.

   (e) ALs calculated from move studies data -- Linear regression analysis on data from samples stored 3 mos @ 25°c/ [redacted] (transferred from 0, 3, and 6 mos at 5° C) was performed and upper 95% Confiedence Bound on the mean predicted level at 21 months at 5° C determined.

Comparison of ALs by (c) and (d)

Degradant	AL by (c)	AL by (d)
[redacted]		

By the same reason as in the KALETRA Capsules, both FDA and Abbott agreed that the looser AL by (c) should be used as the final specification for the oral solution.

10. Labeling -- The following is the agreed upon version of the package insert (PI) and container labels:

   (a) PI Heading

KALETRA™
(lopinavir/ritonavir) capsules
(lopinavir/ritonavir) oral solution

   (b) Description Section

Rearrange inactive ingredients in alphabetic order to comply with USP recommendation.

(c) Recommended storage: Store KALETRA soft gelatin capsules at 36°-46°F (2° C-8°C) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA capsules remain stable until the expiration date printed on the label. If stored at room temperature up to 77°F (25°C), capsules should be used within 2 months.

(d) KALETRA (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL marked dosing cup (80 mg lopinavir/20 mg ritonavir per mL) in the following size:

Recommended storage: Same as for KALETRA capsules.

11. Phase IV Commitment

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

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

Concurrence:
HFD-530/CTL/Miller
HFD-530/CR/Lo

cc:
NDA 21-226 and 21-251
Division File
HFD-530/RRO/Struble
HFD-530/RPM/Belouin
HFD-530/CR/Lo

Record of Teleconference

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM

Date: June 13, 2000

To: David Lepay, M.D., Director, DSI/HFD-340
Tony El Hage, Ph.D., GCPB Reviewer/HFD-340

From: Heidi Jolson, M.D., M.P.H., Director/Review Division/HFD-530 /S/ 6/13/00

Subject: Request for Clinical Inspections for NDA 21226

The following protocols/sites essential for approval have been identified for inspection.
Study M98-863 is the pivotal study in this NDA.

Indication	Pivotal Protocol #	Site (Investigator's Name/Address)
Treatment of HIV Infection	M98-863	Gildon Beal Harbor-UCLA Medical Center Allergy & Immunology 1124 W. Carson St, Box 449 Torrance CA 90509 Number of pts 20
Treatment of HIV Infection	M98-863	Frank Rhame Abbott Northwestern Hospital/Clinical 42 800 E 28th street Minneapolis MN Number of patients 10
Treatment of HIV Infection	M98-863	Gladys Sepulveda Immunology Clinic Ponce University Hospital Road #14 (bo. Machuelo) Ponce, Puerto Rico Number of patients 12
Treatment of HIV Infection	M98-863	Sheetal Sharma Comprehensive Care Center North Broward Hospital District 1101 NW 1st Street Ft. Lauderdale, FL 33311 Number of pts 13
Treatment of HIV Infection	M98-863	James Thommes Pacific Oaks Research 8641 Wilshire Blvd, suite 100 Beverly Hills CA 90211 Number of pts 14

International Inspections: We have requested inspections because (please check appropriate statements):

Note: Due to time constraints no international sites have been recommended for inspection

____ There are insufficient domestic data; or

____ Only foreign data are submitted to support an application; or

____ Domestic and foreign data show conflicting results pertinent to decision-making; or

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

____ Other_____

Five or More Inspections: We have requested these sites for inspection (international and/or domestic) because of the following reasons (justify and prioritize sites).

Please see above. We have no reason to suspect any violations or misconduct, however, these sites were chosen based on the enrollment.

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) August 30, 2000. We intend to issue an action letter on this application by (action goal date) September 8, 2000.

Should you require any additional information, please contact Sylvia Lynche or Kimberly Struble

Concurrence: Jeff Murray, M.D., M.P.H. Medical Team Leader /S/ 6/13/00
Kimberly Struble, Pharm.D., Medical Reviewer 6/13/00
Sylvia Lynche, Pharm.D., Regulatory Project Manager

Distribution: IND/NDA 21226
HFD-530/Division File
HFD-Lynche/Project Manager
HFD-34#/GCPB Reviewer

MESSAGE CONFIRMATION

09/11/00 14:34
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DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
09/11	00'36"	918479378002	CALLING	03	OK	0000

09/11/00 14:33 DAVDP → 918479378002 NO.468 P01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Becky Welch

Fax Number: (847) 937-8002

Date: September 11, 2000

Company: Abbott Labs

No. of pages (excluding cover): 3

Message: Labeling comments for NDA 21-251.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 14, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Ko-yu Lo, PhD, Chemist, HFD-530 /S/ , 9/14/00
Stephen P. Miller, PhD. Chemistry Team Leader, HFD-530 /S/ 9/14/00

NDA: 21-226 and 21-251

Subject: Chemistry Phase 4 requested commitments

1. The applicant commits to reassess the drug substance specification and the drug product specification when the stability studies on the first three commercial scale lots of the capsules have been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed specifications, through a prior approval supplement to NDA 21-226, and this Phase 4 commitment will be satisfied once this supplement is approved.

2. The applicant commits to reassess the drug product specification when the stability studies on the first three commercial scale lots of the oral solution have been completed. During this reassessment, release and stability data from both commercial and representative NDA lots will be considered. The applicant will submit this data, with the proposed specifications, through a prior approval supplement to NDA 21-251, and this Phase 4 commitment will be satisfied once this supplement is approved.

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/

Sylvia Lynche, PharmD
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA 21-226
Division File
HFD-530/Chem/Lo
HFD-530/ChemTL/Miller
HFD-530/RRO/Struble
HFD-530/RMO/Lynche

Facsimile

HFD-530 Lynche

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 11, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Ko-yu Lo, PhD, Chemist, HFD-530 /S/ 9/11/00
Stephen P. Miller, PhD. Chemistry Team Leader, HFD-530 /S/ 9/11/00

NDA: 21-226

Subject: Chemistry Comments

Chemistry Requests for NDA21-226 Lopinavir/Ritonavir Soft Gelatin Capsules, 133.3/33.3 mg

In our 9/1/00 facsimile, we request (5c) additional statistical analysis on data from the move studies. We meant to conduct liner regression analysis of the following data set:

Data at initial
Data for samples stored 3 mos @25° C. ——— (transferred from 3 mos @ 5° C)
Data for samples stored 3 mos @25° C. ——— (transferred from 6 mos @ 5° C)
Data for samples stored 3 mos @25° C. ——— (transferred from 9 mos @ 5° C)

Please carry this analysis for the 5 individual and total ICH Related Substances for ritonavir (see attached exampie of graphic analysis), with pooling if appropriate.

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/
Sylvia Lynche, PharmD
Regulatory Management Officer
Division of Antiviral Drug Products

___1___ page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

cc:
Original NDA 21-226
Division File
HFD-530/Chem/Lo
HFD-530/ChemTL/Miller
HFD-530/RRO/Struble
HFD-530/RMO/Lynche

Facsimile

HFD-530

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service Lynche

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 11, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Ko-yu Lo, PhD, Chemist, HFD-530 /S/ 9/11/00
Stephen P. Miller, PhD. Chemistry Team Leader, HFD-530 eso 9/11/00

NDA: 21-251

Subject: Chemistry Requests

Chemistry Requests for NDA21-226 Lopinavir/Ritonavir Oral Solution, 80 mg/20 mg/mL

1. Reprocessing operation -- Lot # 62-638-AR-XX was prepared with low ethanol in support of reprocessing necessitated by low ethanol. Please identify the elapsed time for this lot to support the proposed 6 months elapsed time.

2. Drug product specification and stability –

a) Please add the following specifications to the product regulatory specification (Document PRS.03956): "color" in Physical Examination, "aerobic microbial counts", and "lopinavir ICH Total Related Substances".

b) Process control limit (PCL) – On p.7 of your email response (9/7/00) for the capsule product, you indicated that the upper tolerance limit $X_u = X_{ave} + Ks$ where X_{ave} and s are estimates of the mean and standard deviation computed from a sample size of n, and K (20, 0.95, 0.999) = 4.319. We recommend that Mean +3s as recommended in ICH (Q6A) be used to calculate X_u .

c) Acceptance limits (AL) for ritonavir related substances -- This is the same question we asked for clarification for the capsule product.

You indicated (R&D/00/148, Vol.7, p.58) that the proposed acceptance limits for the five related substances are calculated as follow: The upper 95% confidence limit after 21 months at 5° C (extrapolated based on 6 months data) was added to the upper 95% confidence limit after 3 months at 25° C/[redacted] (actual 6 month data). The sum of these was then added to the process control limit. However, FDA statistician confirmed us that confidence limits cannot add up.

You indicated (9/7/00 email response) that acceptance limit and process control limit were calculated as follows:

(i) PCS (process control limit) = upper tolerance limit + contribution from oleic acid

(ii) Proposed stability acceptance upper limit (AL) = Y +se (Y) * t (0.95, df)

Y = PCS +S1*T1 + S2*T2
PCS = proposed process control specification

se(Y) = sqrt[RMSE^2 + (T1*se(S1)^2 + (T2*se(S2))^2]
se (Y) = analytical error in the initial test result used to release the lot as well as the standard error of estimates in S1 and S2

In this model, if PCS already takes into account of variability (Item 2b above) please explain the need of including an error term for release data in se (Y).

Please identify the contribution from placebo (%) for each individual related substance.

c) We recommend that lopinavir ICH Total Related Substances be included in your proposed Post Approval Stability protocols

3. Storage recommendation -- For patient convenience, we are considering the possibility of two months at 25° C after dispensing. Please indicate whether this may create problem for you.

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/
Sylvia Lynche, PharmD
Regulatory Management Officer
Division of Antiviral Drug Products

cc:
Original NDA 21-226
Division File
HFD-530/Chem/Lo
HFD-530/ChemTL/Miller
HFD-530/RRO/Struble
HFD-530/RMO/Lynche

Facsimile

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09/11/00 14:33 DAVDP → 918479378002 NO.468 D01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Becky Welch

Fax Number: (847) 937-8002

Date: September 11, 2000

Company: Abbott Labs

No. of pages (excluding cover): 3

Message: Labeling comments for NDA 21-251.

MESSAGE CONFIRMATION

08/31/00 14:40
ID=DAVDP

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
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08/31/00 14:39 DAVDP → 918479378002 NO.435 P01

Division of Antiviral Drug Products (DAVDP)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

TELEFACSIMILE TRANSMISSION RECORD

To: Becky Welch

Fax Number: (847) 937-8002

Date: August 30, 2000

Company: Abbott Labs

No. of pages (excluding cover): 3

Message: Follow-up to 8/31/00 e-mail