COPY

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 1, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Ko-yu Lo, PhD, Chemist, HFD-530 /S/ 9/1/00
Stephen P. Miller, PhD. Chemistry Team Leader, HFD-530 /S/ 9/1/00

NDA: 21-226

Subject: Chemistry Requests

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

With regard to lopinavir drug substance, please clarify the following issues.

1. Table 3 Clinical Drug Substance Specifications Testing Summary (—/00/146, Vol, 4, p. 208)

a) Please explain why the numbers/levels of related substances (individual and total) in Lots 53-071-CA, 54-309-TL, 54-312-TL, and 57-412-TL were greater compared with the majority of lots listed in this table. Were these lots manufactured using the same controls (in-process) as the rest of the lots?

b) Does the value reported as "-" mean "not detected"? How was the level of total related substances calculated?

c) Lots #34-506-VF, 35-507-VF and 36-603-VF are early pilot scale (20 kg) batches. Please reanalyze the related substances (individual and total) and moisture data with production scale lots including those manufactured after 1/00. We recommend that the DS specification be based upon production scale material.

2. Table 8 Statistical Analyses and Specifications for Related substances (R&D/00/146, Vol. 4, p.217)

For impurities —— that have never been detected in the DS lots, we recommend a specification of 0.1% instead of the proposed 0.2%.

3. —/00/139 (Drug Substance Stability) summarized the results of potency, impurities, and moisture. No stability protocol was included in the NDA to show whether other parameters of the drug substance

were also monitored. Please provide a Post Approval Stability Protocol for lopinavir drug substance.

With regard to the soft gelatin capsules

4. Please provide the amounts of ingredients per a typical commercial scale batch

5. On DP specifications & stability (/00/147)

a) Related substance for lopinavir -- Please add a specification of "total degradants" (see Impurity in Drug Product) in Table 1 Acceptance/Release Specifications for lopinavir/ritonavir soft gelatin capsules.

b) We are aware of the complexity of the method to measure related substances in the soft gelatin capsules and appreciate your effort to resolve the problem of oleic acid interference with ritonavir degradation products. Please explain how "tolerance", "contribution from oleic acid" and " process control limits" was calculated in Table 14, and 15.

c) Acceptance limits for ritonavir related substances -- We recommend that you perform additional statistical analysis on data from the move studies. Please assess the poolability of the bottle and blister data before calculating the confidence limits. Please provide graphical display of the data sets with linear regression and upper 95% confidence intervals for and total ICH related substances. We wish to consider the upper 95% confidence limits at the 21 months time point in the move studies (21 mos @ 5deg C + 3 mos @ 25deg C/ when setting the acceptance limits.

You indicated (p.277) that the proposed acceptance limits for the five related substances are calculated as follow: The upper 95% confidence limit after 21 months at 5deg C (extrapolated based on 9 months data) was added to the upper 95% confidence limit after 3 months at 25deg C. (actual 6 month data). The sum of these was then added to the process control limit. Table 17 presented this sum as "increase on stability (21 mos @ 5deg C + 3 mos @ 25deg C). Please provide an example to explain how this increase was calculated. For example, was the initial value subtracted from the later time point to obtain the increase.

e) We recommend that the following parameters be included in your proposed Post Approval Stability Protocols: (i) total degradants for lopinavir, and (ii) propylene glycol content.

6. Storage recommendations -- Please explain your reason for selecting a maximum of 42 days at 25deg C after dispensing.

7. The NDA Method Validation Package does not contain analytical methods for lopinavir drug

substance. Please submit two copies of the analytical methods and provide information regarding the available quantities of standards and samples.

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/ ' '

for.

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

. Jiatric Dosing Guidelines (draft)

For children 6 months to 12 years of age:

Weight (kg)	Weight (lbs)	Dose (mg/kg)*	Volume of oral solution (80mg lopinavir/20mg ritonavir per mL)	Estimated dose in mg/m^2 based on BSA**
Without nevirapine or efaverinz				
' to < 15 kg	—	12mg/kg		
7 to 10 kg	15 to 22 lbs		1.25 mL	*273-215*
>10 to 15 kg	>22 to 33 lbs		1.75 mL	*290-221*
5 to < 40 kg		10 mg/kg		
>15 to 20 kg	> 33 to 44 lbs		2.25 mL	*295-231*
>20 to 25 kg	> 44 to 55 lbs		2.5 mL	*252-230*
>25 to 30 kg	> 55 to 66 lbs		3.0 mL	*250-225*
>30 to 40 kg	> 66 to 88 lbs		3.5 mL	*259-240*
>40 kg	> 88 lbs	adult dose	5 mL (or 3 capsules)	*312-230*

Weight (kg)	Weight (lbs)	Dose (mg/kg)*	Volume of oral solution (80mg lopinavir/20mg ritonavir per mL)	Estimated dose in mg/m² based on BSA
With nevirapine or efaverinz				
' to < 15 kg		13mg/kg		
7 to 10 kg	15 to 22 lbs		1.5 mL	*328-258*
>10 to 15 kg	>22 to 33 lbs		2.0 mL	*332-252*
5 to < 50 kg	—	11 mg/kg		
>15 to 20 kg	> 33 to 44 lbs		2.5 mL	*327-257*
>20 to 25 kg	> 44 to 55 lbs		3.25 mL	*327-299*
>25 to 30 kg	> 55 to 66 lbs		4.0 mL	*334-300*
>30 to 40 kg	> 66 to 88 lbs		4.5 mL	*333-309*
>40 to 50 kg	> 88 to 110 lbs		5.0 mL (or 3 capsules)	*311-267*
· 50 kg	> 110 lbs	adult dose	6.5 mL (or 4 capsules)	*346-301*

= dosing based on the lopinavir component of lopinavir/ritonavir solution (80mg/20mg per mL)
' = for reference only and will not be included in the label. Target mg/m² doses were 230/57.5 mg/m² without nevirapine or efaverinz and 300/75 ·-² with nevirapine or efaverinz.
Use adult dosage recommendations for children > 12 years of age

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

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MESSAGE CONFIRMATION

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

TELECOPIMILE TRANSMISSION RECORD

To: Becky Welch

Fax Number: (847) 937-8002

Date: August 30, 2000

Company: Abbott Labs

No. of pages (excluding cover): 2

Message: Labeling comments for NDA 21-226.

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: August 31, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530 /S/ 8/31/00
Jooran Kim, Ph.D., Pharmacokinetics Reviewer, HFD-530 8/31/00
Jeff Murray, MD, Medical Team Leader, HFD-530 /S/ 8/31/00

NDA: 21-226 /S/

Subject: Pediatric Dosing Table

The attached is a copy of the e-mail document sent to you on August 31, 2000.

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.

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

'ediatric Dosing Guidelines (draft)

or children 6 months to 12 years of age:

Weight (kg)	Weight (lbs)	Dose (mg/kg)*	Volume of oral solution (80mg lopinavir/20mg ritonavir per mL)	Estimated dose in mg/m² based on BSA**
'ithout nevirapine or efaverinz				
to < 15 kg		12mg/kg		
7 to 10 kg	15 to 22 lbs		1.25 mL	*273-215*
>10 to 15 kg	>22 to 33 lbs		1.75 mL	*290-221*
to < 40 kg		10 mg/kg		
>15 to 20 kg	> 33 to 44 lbs		2.25 mL	*295-231*
>20 to 25 kg	> 44 to 55 lbs		2.5 mL	*252-230*
>25 to 30 kg	> 55 to 66 lbs		3.0 mL	*250-225*
>30 to 40 kg	> 66 to 88 lbs		3.5 mL	*259-240*
40 kg	> 88 lbs	adult dose	5 mL (or 3 capsules)	*312-230*

Weight (kg)	Weight (lbs)	Dose (mg/kg)*	Volume of oral solution (80mg lopinavir/20mg ritonavir per mL)	Estimated dose in mg/m^2 based on BSA
/ith nevirapine or efaverinz				
to < 15 kg		13mg/kg		
7 to 10 kg	15 to 22 lbs		1.5 mL	*328-258*
>10 to 15 kg	>22 to 33 lbs		2.0 mL	*332-252*
; to < 50 kg		11 mg/kg		
>15 to 20 kg	> 33 to 44 lbs		2.5 mL	*327-257*
>20 to 25 kg	> 44 to 55 lbs		3.25 mL	*327-299*
>25 to 30 kg	> 55 to 66 lbs		4.0 mL	*334-300*
>30 to 40 kg	> 66 to 88 lbs		4.5 mL	*333-309*
>40 to 50 kg	> 88 to 110 lbs		5.0 mL (or 3 capsules)	*311-267*
50 kg	> 110 lbs	adult dose	6.5 mL (or 4 capsules)	*346-301*

: dosing based on the lopinavir component of lopinavir/ritonavir solution (80mg/20mg per mL)
= for reference only and will not be included in the label. Target mg/m^2 doses were 230/57.5 mg/m^2 without nevirapine or efaverinz and 300/75 m^2 with nevirapine or efaverinz.
:: Use adult dosage recommendations for children > 12 years of age

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

From: Sylvia D. Lynche, PharmD

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Concurrence:
HFD-530/MTL/Murray- /S/ 8/31/00
HFD-530/BiopharmTL/Reynolds 8/31/00
HFD-530/RPM/Carmouze

cc:
Original NDA 21-226
Division File
HFD-530/RMO/Lynche
HFD-530/RRO/Struble
HFD-530/BiopharmTL/Reynolds
HFD-530/Biopharm/Kim

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/S/ 8/31/00

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TELEFACSIMILE TRANSMISSION RECORD

To: Becky Welch

Fax Number: (847) 937-8002

Date: August 15, 2000

Company: Abbott Labs

No. of pages (excluding cover): 5

Message: Labeling comments for NDA 21-226.

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: August 30, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530 /S/ 8-30-00
Steve Miller, Ph.D., Chemistry Team Leader, HFD-530 /S/ 8/30/00
Ko-Yu Lo, Ph.D., Chemistry Reviewer, HFD-530 /S/ 8/30/00
Jeff Murray, MD, Medical Team Leader, HFD-530 /S/ 8/30/00

NDA: 21-226

Subject: CMC and Biopharmaceutics Requests for Information

The following requests are on behalf of Drs. Lo and Reynolds and are directed towards the submission dated July 21, 2000.

1. Your submission dated July 21, 2000 does not include the data needed for a Biopharmaceutics review of the dissolution method and specification for KALETRA capsules. Additional data, as indicated below, are needed as soon as possible. It will not be possible to complete the Biopharmaceutics review without these data. Please try to submit this information by September 1, 2000. If any of the requested data have been submitted previously, please indicate the NDA volume number or IND serial number where they can be located.

2. Please submit the rationale for selecting the dissolution method for KALETRA capsules. Please also include profiles for all media and methods that were evaluated. Mean profiles are acceptable.

3. Please submit dissolution profiles, including individual dosing unit data (n=12), using the selected medium and method. These profiles should be taken from batches that were used in both pharmacokinetic and efficacy studies.

4. Please submit validation data for the dissolution method.

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

Concurrence:
HFD-530/MTL/Murray-
HFD-530/BiopharmTL/Reynolds /S/ 8/31/00
HFD-530/CHEMTL/Miller
HFD-530/CHEM/Lo
HFD-530/RPM/Carmouze

cc:
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HFD-530/RMO/Lynche
HFD-530/RRO/Struble
HFD-530/BiopharmTL/Reynolds
HFD-530/CHEM/Lo

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/S/ 8/31/00

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: August 7, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Kim Struble, PharmD, Regulatory Reviewer, HFD-530
Kellie Reynolds, PharmD, Biopharmaceutics Team Leader, HFD-530

NDA: 21-226 /S/ 8-7-00

Subject: Labeling comments for NDA 21-226.

Listed below are the Clinical and Biopharm comments for drug interactions in the Warning and Precaution sections. Please note that the Biopharm review is not complete and additional comments for these sections may be forwarded at a later time.

WARNINGS:

Drug Interactions:

KALETRA is an inhibitor of the P450 isoform CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **Pharmacokinetics**: Drug-Drug Interactions and **Precautions:** Table 5 Drugs That Should Not Be Coadministered With KALETRA and Table 6: Established and Other Potentially Significant Drug Interactions

Remove rifampin from Warnings (see Table 5)

Precautions:

Drug Interactions

KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both *in vitro* and *in vivo*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong its therapeutic and adverse effects (see Table 6 *Established and Other Potentially Significant Drug Interactions*:). Agents that are extensively metabolized by CYP3A and have high first pass

metabolism appear to be the most susceptible to large increases in AUC (>3-fold) when co-administered with KALETRA.

KALETRA is metabolized by CYP3A. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see Table 6: *Established and Other Potentially Significant Drug Interactions*:). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase KALETRA plasma concentrations.

Drugs that are contraindicated and not recommended for coadministration with KALETRA are included in Table 5: Drugs That Should Not Be Coadministered with KALETRA. 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.

Table 5: Drugs That Should Not Be Coadministered With KALETRA

Drug Class/Drug Name:	**Clinical Comment**
Antiarrhythmics: Flecainide, propafenone	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Antihistamines: astemizole, terfenadine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Antimigraine: dihydroergotamine, ergotamine	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors
GI motility agent: Cisapride	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Herbal Products: **St. Johns wort**	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors

HMG Co-Reductase Inhibitors: Lovastatin, simvastatin	P tential for serious reactions such as risk of myopathy including rhabdomyolysis
Neuroleptic: pimozide	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias
Sedative/hypnotics: midazolam, triazolam	**CONTRAINDICATED** due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression

Table 6: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction
(See Clinical Pharmacology for Magnitude of Interaction, Tables 1 and 2)

Drug Name/Class	Effect on Concentration	Clinical Comment
Antiarrhythmics: Amiodarone, bepridil, lidocaine (systemic) and Quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co administered with KALETRA, if available
Anticonvulsants: phenobarbital, phenytoin, bamazepine	↓Lopinavir	Use with caution. KALETRA may not be effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly
Cholesterol-lowering Agents: Atorvastatin* Cerivastatin	↑ Cholesterol-lowering agents	Use lowest possible dose of atorvastatin or cerivastatin with careful monitoring, or consider alternative HMG-CoA reductase inhibitor such as pravastatin or fluvastatin in combination with KALETRA
Didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA (given with food).
Dexamethasone	↓Lopinavir	Use with caution. KALETRA may not be effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly
Dihydropyridine calcium channel blockers (e.g. felodipine, nifedipine, nicardipine)	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended
Disulfiram/ etronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with

		disulfiram or other drugs that produce this reaction (e.g., metronidazole).
HIV-Protease Inhibitors*	↑Amprenavir ↑Indinavir ↑Nelfinavir ↑Saquinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established
HIV Protease Inhibitors: Ritonavir	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established
Immunosuppressants: Cyclosporine, tacrolimus, rapamycin	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with KALETRA
Ketoconazole*	↑Ketoconazole	High doses of ketoconazole (> 200 mg/day) are not recommended.
Methadone	↓Methadone	Dosage of methadone may need to be increased during concurrent KALETRA.
Non-nucleoside Reverse Transcriptase Inhibitors:* Efavirenz Nevirapine	↓Lopinavir	Consider increasing KALETRA dose to 533/133 mg (4 capsules) BID during efavirenz or nevirapine co-administration in multiple protease inhibitor-experienced patients. (see DOSAGE AND ADMINISTRATION) NOTE: Efavirenz and nevirapine induce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with KALETRA.
Non-nucleoside Reverse Transcriptase Inhibitors:: Delavirdine	↑ Lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established
Oral Contraceptives*	↓Ethinyl estradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and KALETRA are co-administered.
Rifabutin*	↑Rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg /day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse

		events is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored

** (See Clinical Pharmacology for Magnitude of Interaction, Tables 1 and 2)*

Other Drugs:

Drug interaction studies reveal no clinically significant interaction between KALETRA and pravastatin, stavudine or lamivudine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, clarithromycin, azithromycin, erythromycin, itraconazole (doses ≤200 mg/day), or fluconazole

Zidovudine and Abacavir: KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

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

Concurrence:
HFD-530/BTL/Reynolds- /S/ 8-7-00
HFD-530/RR/Struble-

cc:
Original NDA 21-226
Division File
HFD-530/RMO/Lynche
HFD-530/RRO/Struble
HFD-530/BTL/Reymolds

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MESSAGE CONFIRMATION

07/19/00 14:07
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DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
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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: July 19, 2000

Company: Abbott Labs

No. of pages (excluding cover): 7

Message: Statistical comments for NDA 21-226.

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: July 19, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Greg Soon, PhD, Statistical Reviewer,HFD-530 /S/ 7/19/00

Through: Girish Aras, PhD, Statistical Team Leader, HFD-530 /S/ 7/19/00

NDA: 21-226

Subject: Request for additional statistical analysis.

Recently, the DAVDP has modified the definition of time to virologic failure.

It is recommended that time to virologic failure be computed using the following algorithm:

a. All available visits, including off-schedule visits and post Week 48 visits, should be used for the calculation. For the b and c below, discard all visits with no observed viral load.

b. Subjects who never achieved confirmed <LOQ (two consecutive visits <LOQ) before any of the following events will be considered to have failed at time 0.
   i. Death
   ii. HIV disease progression
   iii. Discontinuation or switching of study medications. Temporary discontinuation or dose reduction of study medications may be ignored. Discontinuation or dose reduction of background therapies in blinded studies can be ignored. The handling of other changes in background therapies should be pre-specified in the protocol with FDA consent.
   iv. Last available visit

c. All other subjects will have achieved confirmed <LOQ status at the first of the 2 consecutive visits below LOQ. Time to failure = the earliest of the choices below, with modification specified in d:
   i. Time of death or HIV disease progression.
   ii. Time of the event as described in b.iii.
   iii. Time of loss to follow-up
   iv. Time of Confirmed >LOQ after achieving confirmed <LOQ. Confirmed >LOQ is defined as two consecutive levels greater than LOQ or one visit greater than LOQ followed by events defined in i, ii, iii, and database closure.

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

is replaced by the time of the first such missing visit.

See examples attached in another document, which may clarify some details.

Perform the following calculations using LOQ= [redacted] and then LOQ= [redacted] For double-blind studies, use all subjects randomized who took at least one dose of study medication as the analysis population. For other studies, use all subjects randomized.

Please complete the request by 7/24/2000. To save time, you may send the results electronically first.

Please conduct the following analyses:

1. Calculate time to virologic failure based on the new algorithm and plot the survival curves.

2. For any visit, subjects with the following events before or at the visit will be regarded as failures for that visit:
   a. Never taken study medication (for non double blind studies)
   b. Death
   c. Disease progression
   d. Discontinuation of the treatment
   e. Lost to follow up
   f. Have not achieved confirmed <LOQ status or achieved confirmed <LOQ status but rebounded (two consecutive > [redacted] copies/mL, or one > [redacted] copies/mL if last available visit or if followed by events a, b, c or d).

Other subjects will be regarded as responders. Therefore, responders are those who have achieved confirmed viral load <LOQ but have not become a virologic failure according to the new definition for virologic failure.

Please calculate the response rate for each visit and conduct the primary analyses.

3. Plot the response rates over time and summarize the rates in tables. Graphs and tables should be provided to allow modifications by the reviewers. For example, word tables and excel/powerpoint graphs are fine.

4. Classify Week xx failures into the following categories according to the "primary" reason for the earliest failure:
   Viral rebounder, or Discontinued due to viral rebound
   Never confirmed <LOQ through Week xx
   Death
   HIV disease progression
   Discontinued due to Adverse Events
   Discontinued due to other reasons, including lost to follow ups
   Never initiated treatment

where xx=24, 48 and 72 when applicable. See #7 below for details.

The primary reason should be the most serious event related to the failure. For example, a subject discontinued due to AE but died later due to this particular AE should be regarded as death, not discontinued due to AE.

5. Produce a table of following format based on the results in 4:

Week xx Status	Kalatra N=	Nelfinavir N=
Responder*[a]	xx% (xx%)	xx% (xx%)
Virologic failure*[b]	xx% (xx%)	xx% (xx%)
Death or disease progression	xx% (xx%)	xx% (xx%)
Discontinued due to Study drug or nelfinavir AE	xx% (xx%)	xx% (xx%)
Discontinued due to other AE	xx% (xx%)	xx% (xx%)
Discontinued due to others*[c]	xx% (xx%)	xx% (xx%)
Never initiated treatment	xx% (xx%)	xx% (xx%)

*[a]: **Subjects achieved virologic response (two consecutive viral load <400 (<50) copies/mL) and maintained it to Week xx.**
*[b]: Includes viral rebound and failing to achieved confirmed <400 (50) copies/mL through Week xx.
*[c]: Includes lost to follow up, non-compliance, withdraw and pregnancy.

6. SAS programs together with dataset should be submitted. All programs, including the ones used to derive patient status, should be submitted. Make sure the dataset contains the following information: Baseline info; demographic info; death, disease progression info (time relative to treatment initiation, details), permanent discontinuation of Kalatra and Nelfinavir (time relative to treatment initiation and reasons), time to adding or switching to a new background therapy, HIV viral load and CD4 info at weeks 24, 48 and 72 when applicable; derived variables for the above analysis including time to virologic response, time to virologic failure, reasons for failure (variables defined in 4 and 5 above).

7. Studies covered by this request: M97-720 at Weeks 48 and 72 and M97-765 at Weeks 48 and 72.

8. If there is anything unclear, please contact us as soon as possible.

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

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

Concurrence:
HFD-530/STL/Aras-
HFD-530/SR/Soon-
HFD-530/RRO/Struble- 7/19/00
HFD-530/MOTL/Murray- 7/19/00

cc:
Original NDA 21-226
Division File
HFD-530/RMO/Lynche
HFD-530/RRO/Struble
HFD-530/MO/Murray
HFD-530/STL/Aras
HFD-530/SR/Soon

Facsimile

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: July 17, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Julian O'Rear, PhD, Microbiology Reviewer,HFD-530

Through: Lauren Iacono-Connors,PhD, Microbiology Team Leader, HFD-530

NDA: 21-226

Subject: Microbiology comments for studies M98-957 and M98-765.

---

1. You identify eleven mutations associated with reduced *in vitro* phenotypic susceptibility to ABT-378/r by statistical analyses of genotypic and phenotypic data from studies M97-765 and M98-957. The data from study M97-765 were obtained using the [redacted] assay and the data from M98-957 were obtained using the [redacted] assay. These assays utilize different wildtype or baseline viruses, pHXB2 and pNL4-3 respectively, which may differ in their resistance to ABT-378/r. In addition, these assays may not have the same linearity. Please describe how these data were normalized prior to combining them for the statistical analysis.

2. Study M98-957 subjects had on average been previously treated with 3 protease inhibitors while study M97-765 subjects had failed treatment with a single protease inhibitor. An analysis of the genotypic and phenotypic data from M98-957 alone may identify many of the eleven mutations associated with reduced *in vitro* phenotypic susceptibility. Please consider submitting such an analysis.

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.

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

Concurrence:
HFD-530/MTL/Iacono-Connors-
HFD-530/MR/O'Rear-
HFD-530/RRO/Struble-
HFD-530/MOTL/Murray- eso 7/17/00

cc:
Original NDA 21-226
Division File
HFD-530/RMO/Lynche
HFD-530/RRO/Struble
HFD-530/MO/Murray
HFD-530/MTL/Iacono-Connors
HFD-530/MR/O'Rear

Facsimile

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: July 10, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

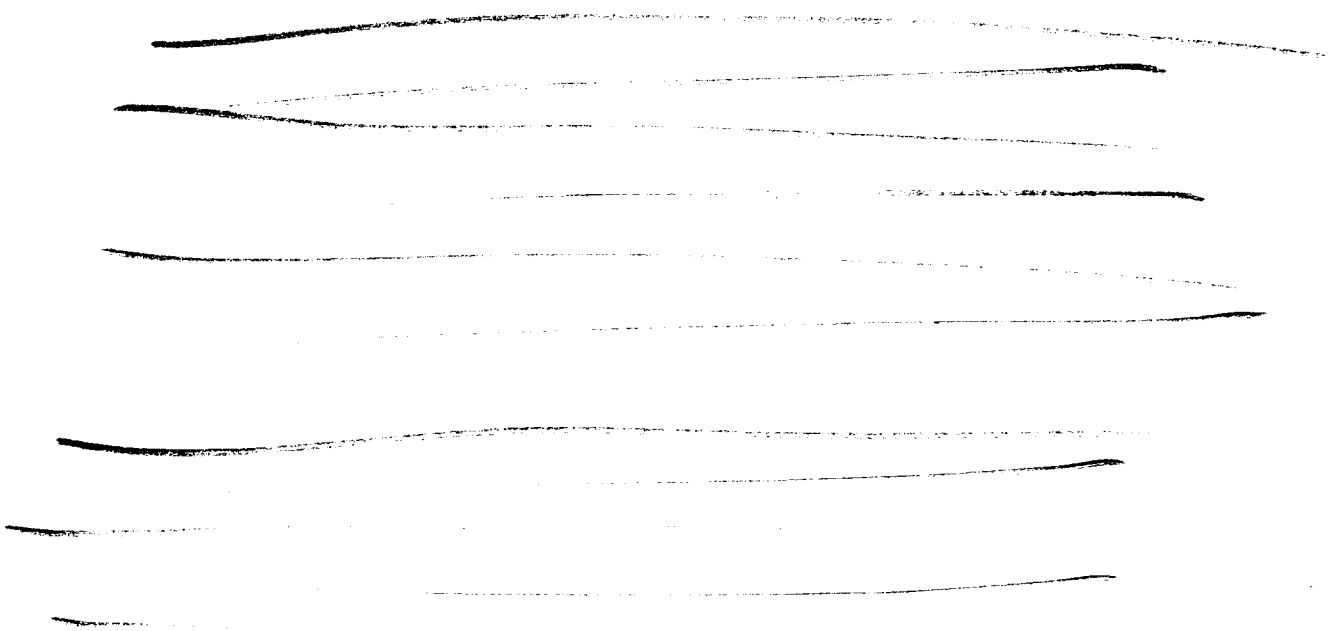
From: Kim Struble, PharmD, Regulatory Reviewer, HFD-530

Through: Jeff Murray, MD, Medical Team Leader, HFD-530

NDA: 21-226

Subject: Labeling comments for NDA 21-226.

Labeling comments:



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

Concurrence:
HFD-530/MTL/Murray-
HFD-530/RR/Struble-

cc:
Original NDA 21-226
Division File
HFD-530/RMO/Lynche
HFD-530/RRO/Struble
HFD-530/MO/Murray

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: April 28, 2000

To: Becky Welch, Associate Director, PPD Regulatory Affairs

Address: Abbott Laboratories

From: Julian O'Rear, PhD, Microbiology Reviewer,HFD-530 /S/

Through: Lauren Iacono-Connors,PhD, Microbiology Team Leader, HFD-530 /S/

NDA: 21-226

Subject: Microbiology request to an electronic format for studies M98-957 and M98-765.

In your Pre-Meeting Package dated March 14, 2000 you refer to phenotypic and genotypic analyses of baseline viruses from Study M98-957. We are looking forward to reviewing these data. Study M98-957 appears to be similar in design to Study M97-765 (Virology Reports #3 and #4, Preclinical section – Vol. 40 and 43, submitted 12/28/99 and 3/31/00). To expedite the review of your submission, it would be helpful to receive in electronic spreadsheet form the M98-957 data equivalent to the M97-765 data listed below.

Please use one row for each patient and the information in the following columns: patient #, previous protease inhibitors (I, N, S, R, A), protease cleavage site at end of NC (+,-), protease cleavage site at the end of the 1 kDa fragment (+,-), log drop in RNA at 2 weeks, change in ABT-378 EC_{50}, IDV EC_{50}, NFV EC_{50}, RTV EC_{50}, SQV EC_{50}, amino acid sequence of baseline protease: 1 column/amino acid – blank column space for the WT residue and 1 letter code for the mutant amino acid residue, HIV RNA (log copies/mL) at 24 weeks (400 copies/mL cut-off), HIV RNA (log copies/mL) at 48 weeks (400 copies/mL cut-off), Outcome (blank = response, failure, censored), HIV RNA (log copies/mL) at 24 weeks (50 copies/mL cut-off), HIV RNA (log copies/mL) at 48 weeks (50 copies/mL cut-off), and Outcome (blank = response).

Virology Report #3

Appendix 4 Fold Change in EC_{50} of Protease and Reverse Transcriptase Inhibitors Against M97-765 Baseline Viruses

Appendix 5 HIV Protease and *gag* Cleavage Site Mutations in Baseline Viruses for Study M97-765

Appendix 7 Two Week Viral Load Decline and Baseline Viral Phenotype

Virology Report #4

Appendix 2 Treatment Regimens at Week 24 and Week 48 in Study M97-765

Appendix 3 Baseline Overall Phenotype and Genotype Parameters for Regimen Administered at Week 24 and Week 48

Appendix 4 Baseline Susceptibility to ABT-378 and Genotypic Parameters

Appendix 5 Virologic Outcome at Weeks 24 and 48 (400 copies/ml cut-off)

Appendix 6 Virologic Outcome at Weeks 24 and 48 (50 copies/ml cut-off)

Appendix 7 Baseline Genotype and Virologic Outcomes of Subjects with Three or More Mutations at Amino Acids 10, 54, 71, and 82

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

Concurrence:
HFD-530/MTL/Iacono-Connors
HFD-530/MR/O'Rear
HFD-530/RRO/Struble
HFD-530/MOTL/Murray

cc:
Original NDA 21-226
Division File
HFD-530/RMO/Lynche
HFD-530/RRO/Struble
HFD-530/MO/Murray
HFD-530/MTL/Iacono-Connors
HFD-530/MR/O'Rear

Facsimile

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

NDA: **21-226**

Date: **October 27, 2000**

Drug: **Kaletra™ (lopinavir)**

Sponsor: **Abbott Laboratories**

BETWEEN: **Representatives of DDREII**
Kathleen Uhl, Deputy Director, DDREII
Toni Piazza-Hepp, Associated Director, DDREII
Debra Boxwell, Safety Evaluator, DDREII
Mary Dempsey, Regulatory Health Project Coordinator, DDREII
Carolyn McCloskey, Medical Officer, DDREII

AND: **Representatives of DAVDP**
Debra Birnkrant, M.D, Deputy Division Director, DAVDP
Jeff Murray, MD, MPH, Team Leader, DAVDP
Kim Struble, PharmD, Regulatory Review Officer, DAVDP
Sean Belouin, R.Ph., Regulatory Project Manager, DAVDP

Background: Pre-Approval Safety Conference (PSC) for Kaletra (NDA 21-226), combination lopinavir/ritonavir for the treatment of HIV infection.

Discussion:

1. It was discussed that Kaletra has similar safety concerns as the other protease inhibitors. Some particular safety issues discussed include the occurrence of TTP, thrombocytopenia, and hemolytic anemia seen in the expanded access program but not in clinical studies. Pancreatitis occurred with an incidence of 1%, with some fatalities, however, these cases are difficult to assess causality due to other antiviral therapies including DDI and d4T. Transaminase elevations are common and more so with underlying Hepatitis B and C infections. Preclinical studies demonstrated PR interval lengthening in dogs, and paired EKGs in clinical studies (approx 600 subjects) demonstrated a mean QTc prolongation of 3 ms, which is not included in the label because it was deemed to be clinically insignificant.

2. Further discussion included the "Alert Box" on the unit of use packaging (monthly supply) regarding concerns for drug interactions that instructs the patient to "Find out about drugs that should not be taken with Kaletra". This is an interesting risk management strategy that will be discussed in OPDRA further to see what potential studies can be done to study the effectiveness, impact of "Alert Box", among others.

/S/

Signature, minutes preparer: _____ **Date:** 10/30/00

Concurrence:
HFD-530/DepDivDir/Birnkrant 10/31/00
HFD-530/MOTL/Murray 10/30/00
HFD-530/RRO/Struble-eso-10/30/00

cc:
NDA 21-226
Division File
HFD-530/RRO/Struble

TELECONFERENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

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 ($X_u = X_{ave} + 4.319 \times SD$) 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] Total ICH Ritonavir [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]		
Total ICH-Ritonavir	[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° [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]		
Total ICH Ritonavir	[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 /S/ 10/13/10
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

Record of Teleconference

NDA: **21-226**

Date: **August 22, 2000**

Drug: **Kaletra (lopinavir)**

Sponsor: **Abbott Laboratories**

BETWEEN: **Representatives of Abbott**
Eugene Sun, MD, Antiviral Venture Head
Ms Jeanne Fox, Director, Regulatory Affairs
Ms Rebecca Welch, Associate Director, Regulatory Affairs

AND: **Representatives of DAVDP**
Jeff Murray, MD, MPH, Team Leader
Kim Struble, PharmD, Regulatory Review Officer
Kellie Reynolds, PharmD, Biopharmaceutics Team Leader
Jorran Kim, PharmD, Biopharmaceutics Reviewer
Sylvia Lynche, PharmD, Regulatory Project Manager

Background: Please refer to the submission dated August 2, 2000. This submission provides the sponsors rationale for not including a Box Warning for drug interactions and consideration for removal of antiarrhythmics which are CYP2D6 substrates from the Contraindication Table. Please also refer to the August 22, 2000 email from Rebecca Welsh that provides for the sponsor's position paper regarding the dual protease inhibitor interaction studies.

Discussion:

- It was stated that the sponsor's rationale for not including a Box Warning for drug interactions was reviewed by the clinical and biopharm reviewers. This issue will be discussed with Dr. Jolson.

- Dr. Reynolds requested additional information on the IC50 analysis for lopinavir/ritonavir combination for various CYP enzymes. The sponsor explained the IC50 determination for the lopinavir/ritonavir combinations.

- It was stated that KALETRA's potential to inhibit CYP2D6 would be further discussed within the review team. These discussions will impact the placement of antiarrhythmics that are CYP2D6 substrates in the package insert.

- The sponsor was notified that the division was revising the pediatric dosing table to reflect dosing based on mg/kg vs mg/m^2. The review team will forward these suggestions to Abbott within the week.

Concurrence:
HFD-530/TL/J.Murray- eso 9/21/00
HFD-530/RRO/Struble-eso 9/21/00
HFD-530/BTL/Reynolds-eso 9/18/00
HFD-530/BR/KimJ-eso 9/18/00

cc:
NDA 21226
Division File
HFD-530/RRO/Struble
HFD-530/RPM/Lynche
HFD-530/BR/KimJ

Record of Teleconference

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

NDA: **21-226**

Date: **July 21, 2000**

Drug: **Kaletra (lopinavir)**

Sponsor: **Abbott Laboratories**

BETWEEN: **Representatives of Abbott**
Eugene Sun, MD, Antiviral Venture Head
Richard Rode, PhD, Statistics
Ms Jeanne Fox, Director, Regulatory Affairs
Ms Rebecca Welch, Associate Director, Regulatory Affairs

AND: **Representatives of DAVDP**
Jeff Murray, MD, MPH, Team Leader
Kim Struble, PharmD, Regulatory Review Officer
Sylvia Lynche, PharmD, Regulatory Project Manager

Background: This teleconference was requested by Abbott Laboratories to obtain clarification on the July 10, 2000 and July 19, 2000 facsimiles that was sent to them by DAVDP.

Discussion:

The teleconference began with the discussion of July 10, 2000 facsimile. This facsimile provided labeling comments for NDA 21-226.

Box Warning:

- Abbott stated the drug interaction between nonsedating antihistamines, sedative hypnotics, antirrhythmics, and ergot alkaloid preparations should not be a Black Box warning. They are putting together a response to justify that this information should be included in the Contraindication section only. This response will show that KALETRA looks closer to indinavir with respect to its effect on CyP3A metabolism based on in vitro data.
- Abbott asked what are the main criteria for including drug interactions as a Black Box warning. DAVDP responded that interaction which results in a death or life-threatening reaction may be displayed in a Black Box warning. DAVDP noted a death when ABT-378/ritonavir was co-administered with an ergot alkaloid. Abbott commented that other deaths/serious events have occurred with other protease inhibitors and ergot alkaloids. It was agreed that this would be further addressed.

Contraindications:

- DAVDP commented that the cardio-renal division recommended that flecainide and propafenone be included in the Contraindication section for all protease inhibitors. This issue will discussed further with Dr. Reynolds.

Warnings
Pancreatitis:

- Abbott stated that they have no issue with pancreatitis being moved to the Warning section of the label, but would like to change some of the wording to reflect in the norvir label. They will be sending in suggested wording in a couple of weeks.

Precautions
Hepatitis reaction:

- Abbott stated that the risk of hepatitis reaction should not be in the Precaution section of the label, because study 863 showed a hepatic risk that was identical to nelfinavir. They noted that this risk was not in the nelfinavir label. Abbott found no cases of clinical hepatitis related to ABT-378/ritonavir use. Patients with hepatitis B or C at baseline were at increased risk for developing grade 3 or 4 transaminase elevations. They also stated that odds for grade 3 or 4 transaminase elevations are greater for patients on Viracept. They will propose wording on the hepatic reaction for DAVDP to review.

Other Issues:

- DAVDP noted that there have been various discussions in the division to keep astemizole and terfenadine in the label because patients may still be able to obtain these medications.
- In addition, DAVDP stated that Dr. Linda Lewis is still reviewing the ALT toxicity grading scale issue and is obtaining information from DAIDS.

July 19, 2000 facsimile discussion. This facsimile provided comments from the statistical reviewer. This facsimile provided for a modification on the definition of time to virologic failure and requested additional statistical analysis by Abbott.

- DAVDP stated that these comments came about from the traditional approval looking at long term data. Abbott should recalculate time to virologic failure using the new algorithm for the 400/100 mg dose groups only with 72-week data. DAVDP stated that this algorithm was not developed in regards to clinical practice. This algorithm was developed from a conservative approach. In addition, it was noted that antiretrovirals having 48-week (traditional approval) data are currently using this algorithm.

Action Items:

1. Abbott will be providing information to remove the Black Box warning in a couple of weeks.
2. Abbott will provide suggested wording for pancreatitis to reflect the norvir label.
3. Abbott will propose wording on the hepatitis.

Concurrence:
HFD-530/TL/J.Murray- eso 8/2/00
HFD-530/RRO/Struble- eso 8/2/00

cc:
NDA 21226
Division File
HFD-530/RRO/Struble
HFD-530/RPM/Lynche

Record of Teleconference

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Record of Teleconference

NDA: **21-226**

Date: **April 18, 2000**

Drug: **ABT-378/ritonavir capsules**

Sponsor: **Abbott Laboratories**

BETWEEN: Representatives of Abbott
Eugene Sun, MD, Antiviral Venture Head
Barry Bernstein, MD, Associate Medical Director
Scott Brun, MD, Associate Medical Director
Rick Bertz, PhD, Pharmacokinetics
Ann Hsu, PhD, Pharmacokinetics
Marty King,PhD, Statistics
Richard Rode, PhD, Statistics
Dale Kemf, PhD, Virology
Ms Amy Potthoff, Clinical Operations Manager
Ms Jeanne Fox, Director, Regulatory Affairs
Ms Rebecca Welch, Associate Director, Regulatory Affairs

AND: Representatives of DAVDP
Jeff Murray, MD, MPH, Team Leader
Kim Struble, PharmD, Regulatory Review Officer
Heidi Jolson, MD, MPH, Division Director
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Greg Soon, PhD, Statistical Reviewer
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Linda Lewis, MD, Medical Reviewer
Sylvia Lynche, PharmD, Regulatory Project Manager

Background: This teleconference was requested by Abbott Laboratories to discuss their pre-NDA application for ABT-378/ritonavir. Please refer to the March 14, 2000 submission. The sponsor is requesting that the following items be discussed:

I. Questions for resolution regarding the proposed label and ISS/ISE format.

II. Sections of the proposed label which address the Virology, Pharmacokinetics, and Clinical studies.

III. Current status for the ongoing Phase 2 and 3 studies.

Discussion:
It was stated that there would be no formal discussion regarding the proposed label at this time, however general comments were conveyed to the sponsor.

Microbiology

Agenda item 1: Abbott presented an overview of the microbiology section draft labeling and resistance – data.

Response: It was stated that the proposed subheading (Antiviral activity of TRADE NAME in patients failing protease inhibitor therapy and selection of viral resistance during TRADE NAME therapy) in the Microbiology section appear reasonable. However, it will be a review issue to determine if the submitted data will be supportive of these claims. The sponsor was told that the microbiology reviewer has specific additional requests for data to be submitted. A facsimile detailing these requests will follow the teleconference.

Biopharmaceutics

Agenda item 2: Abbott presented an overview of the clinical pharmacology section draft labeling.

Response: The sponsor's proposal to describe ritonavir as a pharmacokinetic enhancer of ABT-378 and to provide pharmacokinetic information about ritonavir in the label to the extent that it is clinically relevant and interpretable is acceptable. In addition, the sponsor's proposal to show effect of other drugs on ABT-378 and not ritonavir pharmacokinetic parameters in the Drug Interaction table is acceptable. Further discussion will occur regarding the amount of data presented in the label for dual protease inhibitor combination regimens. The sponsor's proposal of formally evaluating only ABT-378 in bioequivalence studies is acceptable at this time. Abbott was requested to submit a label showing the Drug Interaction section in a table format using the ritonavir label as an example.

Clinical

Agenda item 3: The efficacy data would include a viral load and CD4 responses through 72 weeks for the ABT-378/ritonavir registration dose of 400/100 mg BID dose in study M97-720 (n= 51) and study M97-765 (n= 34).

Response: A statement in the label about the 72 week data would be acceptable. The statement can include the basic design of the study and that patients were followed out to 72 weeks. It would not be acceptable to present a graph or chart for the 72 week data.

Agenda item 4: The safety data would include pooled adverse event and laboratory data for all doses tested in study M97-720 (n= 100) and study M97-765 (n= 97).

Response: This issue was not adequately discussed with the sponsor. A subsequent teleconference will be held to address this issue.

Agenda item 5: In the Phase 3 M98-863 study, 24 week data from the Roche ultrasensitive assay would be displayed. In the Phase 2 M97-720 and M97-765 studies, 72 week data from the Abbott Laboratories LCx HIV RNA quantitative assay would be displayed.

Response: It would be acceptable to use the Roche ultrasensitive assay, but for the LCx assay Abbott would need to send additional data characterizing the performance characteristics of the Abbott Laboratories LCx HIV RNA quantitative assay as describe in the draft guidance "Clinical Considerations for Accelerated and Traditional Approval of Antiretroviral Drugs Using Plasma HIV RNA Measurements." Abbott stated that viral load samples from studies 720 and 765 were reassayed using the Roche ultrasensitive assay. This data will be submitted in the May submission. The sponsor is not planning to use the LCx assay data to support proposed labeling.

Agenda item 6: The reporting of laboratory abnormalities as adverse events is subjective and variable depending on the investigator. Laboratory abnormalities will handle in a quantitative fashion in a separate table using specific Grade 3 / 4 cutoff criteria included in study protocols.

Response: The sponsor's proposal is acceptable.

Agenda item 7: Phase 1 studies are proposed to be handled by pooling all doses in studies where subjects received only ABT-378/ritonavir (e.g., bioequivalence, etc.) with discussion under a Phase 1 Studies section. All ABT-378/ritonavir dosed used in drug interaction studies would be presented under a separate Drug-Drug Interaction section.

Response: The proposal to pool all phase 1 studies regardless of other agents administered is acceptable.

Agenda item 8: For Phase 2/3 studies, data will be presented for all dose levels of ABT-378/ritonavir for the individual studies: M97-720, M97-765, M98-957, M98-863. Study M98-040 will be addressed in a separate section, as it is conducted in a pediatric population.

Response: It is acceptable to present the data in this matter.

Agenda item 9: The sponsor's proposal to limit the primary pooled analysis to subjects receiving the ABT-378/ritonavir 400/100 mg twice daily dose in ISE is acceptable. In addition, the pooling of data for treatment naïve and treatment experienced patients, both and separately is acceptable. The sponsor was asked to provide a summary table of treatment-emergent AEs >5% incidence not >10% incidence.

Agenda item 10: The primary analyses and additional safety analyses of AE and laboratory data for the ISS as outlined on pages 11 and 12 of the backgrounder is acceptable. In addition, it was suggested that the sponsor conduct analyses on concomitant bilirubin and ALT elevations for each study.

Agenda item 11: The sponsor's proposal to not include results from studies 888, 046, and 056 in the pooled analyses is acceptable.

Other discussion items:

- Abbott will submit the Drug Interaction table in a summary report in June, 2000.
- Abbott will submit serious adverse events by August 7, 2000 in a safety update.
- The ISS report for study 888 will be submitted in June, 2000. Abbott notes that they are still enrolling patients and project full enrollment by early fall.
- Abbott will submit the pediatric study in May, 2000 and will supply two copies.

APPEARS THIS WAY
ON ORIGINAL

Concurrence:
HFD-530/TL/J.Murray- eso 5/19/00
HFD-530/RRO/Struble- eso 5/19/00
HFD-530/MicroR/O'Rear- eso 5/18/00
HFD-530/BR/Rajagopalan- eso 6/1/00
HFD-530/BRTL/Reynolds- KJR 6/6/00

cc:
NDA 21226
Division File
HFD-530/RRO/Struble
HFD-530/MicroR/O'Rear
HFD-530/RPM/Lynche
HFD-530/PTR/Zhang
HFD-530/CR/Lo
HFD-530/BR/Rajagopalan
HFD-530/SR/Soon

Record of Teleconference

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

45 DAY FILING MEETING MINUTES

NDA: 21-226 and 21-251

DATE: July 18, 2000

DRUG: Kaletra (Lopinavir)

SPONSOR: Abbott Laboratories

PARTICIPANTS: Heidi Jolson, M.D., Division Director
Jeff Murray, M.D., Medical Team Leader
Kim Struble, Pharm.D., Regulatory Review Officer
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Walla Dempsey, Ph.D., Deputy Division Director
Sylvia D. Lynche, Pharm.D., Regulatory Management Officer
Dr. Rodriguez, PDIT
David Rader, Center Regulatory Affairs

BACKGROUND: Abbott Laboratories submitted these applications on January 3, 2000 and April 3, 2000 as a rolling NDA. The PDUFA clock started on June 1, 2000. It has a filing date of July 18, 2000 and a user fee date of December 1, 2000. This meeting was held to determine if the application is fileable and for Biopharmceutics to give a summary on the pharmacokinetic studies.

CHEMISTRY:
The application is filable. No comments at this time. Chemistry will be discussing the excipients and the qualification of impurities/degradants at the August 15, 2000 global assessment meeting.

PHARMACOLOGY/TOXICOLOGY:
The application is filable. No comments at this time.

MICROBIOLOGY:
The application is filable. No comments at this time.

CLINICAL/STATISTICS:
The application is filable. No comments at this time.

BIOPHARMACEUTICS:
The application is filable. The Biopharmaceutics reviewer presented a summary of the pivotal drug interaction studies.

Study M96-552- Single dose PK:

a. When administered without ritonavir, ABT-378 exhibits poor and variable absorption.
b. Concomitant administration of ritonavir significantly increases the plasma concentrations of ABT-378 by inhibiting the metabolism of ABT-378.
c. Renal elimination of ABT-378 is a minor pathway. Less than 3% of orally administered drug is eliminated unchanged in the urine.

Study M97-650- Multiple dose PK:

a. When administered with fixed doses of ritonavir, the pharmacokinetic parameters of ABT-378 increase in a less than dose proportional manner.
b. Increasing the dose of ritonavir with fixed doses of ABT-378 results in an increase in exposure to ABT-378. At a dose of 200 mg of ABT-378, increase in ritonavir dose from 50 to 100 mg resulted in an average 60% increase in AUC_{24} of ABT-378. At a dose of 400 mg of ABT-378, the increase in average AUC was 15%.

Study M97-765- phase 2 study:

a. The plasma ABT-378 concentrations were significantly greater than the in vitro protein binding corrected EC_{50} for wild type HIV-1 (~ 0.07 µg/mL).
b. No correlation between ABT-378 plasma concentration and antiviral activity was observed in this study.
c. Since ritonavir concentrations were below its in vitro EC_{50} value, the antiviral activity following administration of ABT-378/ritonavir 400 mg / 100mg can be attributed mainly to ABT-378.

Study M97-723- Mass balance study:

Approximately 10% and 80% of the administered radioactivity was eliminated in urine and feces, respectively. ABT-378 accounted for 22% of the fecal radioactivity. The Sponsor states that some of this could represent unabsorbed drug. Since preliminary observations from other studies indicate that ABT-378 is a substrate of p-glycoprotein, part of the radioactivity could be due to "excretion" into the gastrointestinal tract by this transporter.

Study M97-704- ABT-378/RTV and NVP:

a. The results of this study appear to suggest that the pharmacokinetics of ABT-378,

ritonavir and nevirapine may not be significantly affected by concomitant administration of these drugs. (Note: Small sample size).

b. 9 out of 29 subjects dropped out of the study due to adverse events. According to the Sponsor, in a subsequent study (M97-765), a regimen containing ABT-378/ritonavir and nevirapine was generally well tolerated by 70 HIV-infected patients without any discontinuation attributed to hepatitis or elevated liver function tests.

Study M98-969- oral contraceptives drug interaction:

a. The concentrations of ethinyl estradiol were decreased significantly following concomitant administration of ABT-378/ritonavir. Therefore, oral contraceptives containing ethinyl estradiol should NOT be used as a primary method of birth control by female patients receiving ABT-378/ritonavir.

b. May ask for phase 4 commitment for further studies for drug interaction with birth control pills.

Study M97-704- ABT-378/RTV – statin interaction:

a. The results of this study indicate that pravastatin (20 mg QD for 4 days) does not affect the pharmacokinetics of ABT-378/ritonavir. Concomitant administration of ABT-378/ritonavir and pravastatin increased the exposure to pravastatin and its metabolite SQ 31906 by approximately 30%. This is generally not considered to be clinically significant; however, patients receiving a dose of 40 mg QD of pravastatin may be monitored for adverse events.

b. The results of this study indicate that atorvastatin (20 mg QD for 4 days) does not affect the pharmacokinetics of ABT-378/ritonavir. Concomitant administration of ABT-378/ritonavir and atorvastatin results in significant increase in the exposure to atorvastatin. If concomitant administration of ABT-378/ritonavir and atorvastatin is necessary, then the lowest possible dose of atorvastatin (10 mg) should be considered and patients should be carefully monitored for adverse events.

Ketoconazole- ABT-378/ritonavir interaction study:

a. Concomiant administration of ABT-378/ritonavir and ketoconazole results in significant increase (3-fold) in ketoconazole AUC. Ketoconazole did not appear to have a clinically significant effect on the pharmacokinetics of ABT-378/ritonavir. It is recommended that there should be a statement in the Precaution section for monitoring this effect.

M97-085 – ABT-378/RTV, methadone, amprenavir:

a. Concomitant administration of ABT-378/ritonavir and methadone results in a substantial decrease in methadone plasma concentrations. Therefore, the dose of methadone may be adjusted in patients receiving ABT-378/ritonavir.

b. Approximately 20% decrease in exposure to ABT-378 was observed when ABT-378/ritonavir was coadministered with 450 mg or 750 mg of amprenavir. When compared to historical data, C_{max} and AUC values were lower (55% and 18%, respectively) when amprenavir was dosed at 750 mg BID along with ABT-378/ritonavir. While the decrease in ABT-378 concentrations may not be significant, the clinical significance of decrease in amprenavir concentrations may not be significant, the clinical significance of decrease in amprenavir concentrations is not known. Recommend dual protease inhibitor dosing administration in the label.

M98-957- ABT-378/RTV, efavirenz:

Comparison to historical data indicates that the dose of ABT-378/RTV may be increased to 533 mg / 133 mg when dosed with efavirenz. Efavirenz PK was not affected.

M99-107- ABT-378/fifampin:

The results of this study indicate that concentrations of ABT-378 and ritonavir are significantly decreased when administered with rifampin. Recommend in the label not to

administer rifampin with ABT-378.

M99-113- ABT-rifabutin:

The results of this study indicate that the metabolism of rifabutin and 25-O-desacetylrifabutin is inhibited by concomitant administration of ABT-378/ritonavir. Dose adjustment is required for rifabutin. Concomitant administration of rifabutin did not have an effect on the pharmacokinetics of ABT-378/ritonavir. Recommend as a phase 4 commitment to look at dose adjustment studies.

M98-940- Pediatric PK:

At a dose of 300 / 75 mg/m2 BID, the exposure to ABT-378 was higher than the protocol defined upper boundary (130%) of average adult exposure at a dose of 400 / 100 mg BID. According to the Sponsor, this did not result in a higher incidence of clinically significant adverse events.