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APPLICATION NUMBER:

21-226/S-003

21-251/S-004

MICROBIOLOGY REVIEW

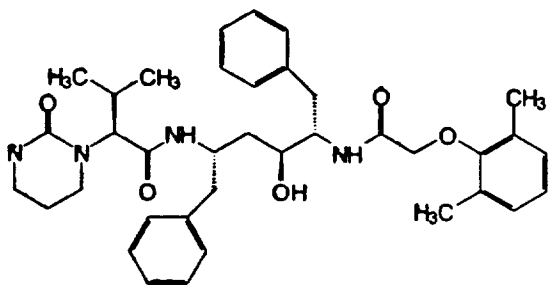
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW

NDA#: N021226 **SN** (SLR-003) **DATE REVIEWED:** 1/4/02

REVIEWER: Julian J. O'Rear, Ph.D.
Date Submitted: 3/19/01 **Date Assigned:** 3/26/01
Date Received: 3/20/01

Sponsor: Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-3500

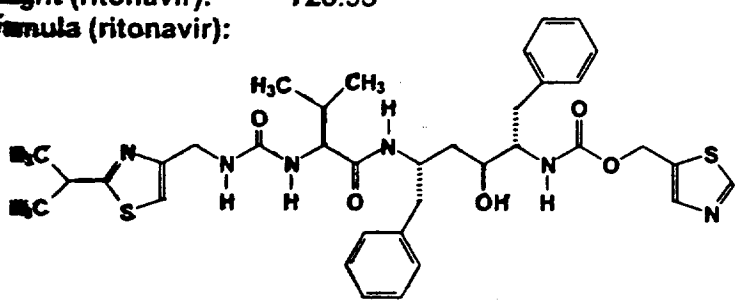
Product Names: lopinavir, ABT-378, Abbott 157378
Chemical Name: [1S-[1R*,(R*),3R*,4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1- (phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide.
Structural Formula:



ABT-378

Empirical Formula: $C_{37}H_{48}N_4O_5$
Molecular Weight: 628.82
Drug Class: Antiviral
Indication: Treatment of HIV infection
Dosage Form; Route of administration: Tablets and soft gel capsule/Oral

Lopinavir co-dosed with ritonavir, an inhibitor of CYP3A4.
Chemical Name (ritonavir): 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8.11-*bis*(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)].
Empirical Formula (ritonavir): $C_{37}H_{48}N_6O_5S_2$
Molecular Weight (ritonavir): 720.95
Structural Formula (ritonavir):



RITONAVIR

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW
NDA#: N021226 **SN** (SLR-003) **DATE REVIEWED:** 1/4/02

Supporting Documents: IND#'s [redacted] and supplements and amendments; NDA #21-226.000.
Abbreviations: AIDS, acquired immunodeficiency syndrome; APV, amprenavir; BID, *bis in die*; d4T, stavudine; HIV-1, human immunodeficiency virus-1; IDV, indinavir; NFV, nelfinavir; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir; 3TC, lamivudine; TID, *tris in die*; WT, wild type;

BACKGROUND AND SUMMARY

Abbott Laboratories, Inc. has submitted this supplemental NDA for KALETRA (LPV/RTV) containing data from a study of treatment naïve individuals (Study M98-863) and an update of a study of multiple PI-experienced individuals (Study M98-957). Study M98-957 has been reviewed previously (original NDA). Several of the proposed changes to the label incorporate the week 48 data from this study.

Virology Report #8: Analysis of Viral Isolates from Subjects with Plasma HIV RNA ≥400 copies/mL in a Double Blind Phase III Study Comparing ABT-378/RTV plus Stavudine and Lamivudine to NFV plus Stavudine and Lamivudine (Study M98-863)

In this study, the sponsor has utilized a new genotypic definition of resistance to LPV to look for possible resistant HIV-1 in patients experiencing at least one viral load measurement of ≥400 copies/mL between weeks 24 and 48. No LPV-resistant HIV-1 was identified and this was confirmed by phenotypic analysis. These results are not surprising given that few LPV-resistant viruses were identified in another study of treatment naïve individuals (M97-720).

Previously, Abbott had attempted to define genotypic resistance to LPV in a study of treatment naïve subjects looking for new mutations associated with reduced susceptibility to LPV *in vitro* (Study M97-720). However, there were insufficient numbers of individuals failing therapy in this study to conduct an analysis. The sponsor then designed studies of individuals who had previously failed in 1 PI (M97-765) and 3 PI (M98-957) regimens with an aim to provide some insight into baseline mutations associated with reduced susceptibility *in vitro*. Because neither study produced statistically significant associations with mutations, the data from Studies M97-765 and M98-957 were pooled and used to identify 12 PI mutations associated with a poor response: 10, 20, 24, 46, 53, 54, 63, 71, 73, 82, 84 and 90. The identification of mutations in this manner was limited due to genetic linkage and the likelihood that not all possible combinations of so identified mutations were likely to lead to reduced susceptibility. In addition, this analysis was flawed due to the use of different assays for each study [redacted] and the absence of normalization data.

In Study M98-863, genotypic resistance to LPV was defined as the presence of any primary PI mutations associated with reduced susceptibility to PIs (Table 1; from CBER Draft Guidance Document entitled, "Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays: Special Controls") or mutations at the active site (amino acid residues 8, 30, 32, 46, 47, 48, 50, 82, 84, 90). Genotypic resistance to NFV was defined as the presence of the D30N and/or the L90M. Secondary mutations were defined as L10F/I/R/V; K20M/R; L24I, L33F, M36I/V, M46I/L, I54L/T/V, A71L/V/T,

G73A/S/T, V77I, and N88D. The division has not accepted any of the definitions of genotypic resistance to LPV.

Table 1.Mutations Recognized to Confer Clinical Resistance to Protease Inhibitors

Mutation	Resistance Profile	Interpretation
D30N	NFV	As a single mutation confers resistance to NFV
M46I	ALL PIS	Confers resistance in combination with other mutations associated with clinical resistance
G48V	SQV	Confers resistance in combination with other mutations associated with clinical resistance
I50V	APV	Confers resistance usually in combination with other mutations
I54V	ALL PIS	Confers resistance in combination with other mutations associated with clinical resistance
V82 (A/F/T/S)	RTV, IDV, LPV/RTV, NFV, SQV	More strongly associated with IDV, RTV, and LPV; Confers resistance usually in combination with other mutations
I84V	ALL PIS	Confers resistance usually in combination with other mutations
N88D	NFV	
L90M	ALL PIS	More strongly associated with SQV or NFV but in combination with other mutations may confer resistance to all PI

Treatment naïve subjects received LPV/r (400/100 mg BID) or NFV (750 mg TID) in combination with d4T/3TC. Plasma HIV RNA declined below <400 copies/mL in 92 % of LPV patients and 82 % of NFV patients at 48 weeks. Fifty-eight (18%) LPV/r- and 102 (31%) NFV-treated patients had an RNA value ≥400 copies/mL at weeks 24, 32, 40, 48, and of these, 37 and 76 could be amplified for analysis

Genotypic analysis from the 37 LPV/r-treated patients failed to identify any LPV-resistant virus (0%). On the other hand analysis of the 76 NFV-treated patients identified 25 resistant virus isolates (33%). Susceptibility to LPV (<2.5 fold reduced susceptibility) was confirmed by phenotypic testing using the [redacted] HIV assay, as was susceptibility to APV, IDV, LPV, NFV, RTV, and SQV. NFV resistance was not confirmed.

Draft Labeling

[redacted]

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

Comment: The phrase "Genotypic or phenotypic" was removed because the Division does not recognize any of the sponsor's definitions of genotypic resistance to LPV.

Comment: "evaluable" was added for clarification since data were not available for all patients.

Comment: Development of resistance to KAKETRA in pediatric patients appeared to be similar to that in adults. There were few treatment failures in the treatment naïve pediatric group as seen in adult treatment naïve patients (study 720).

Comment: "therapy" was changed to "therapies" to reflect the fact that patients in Study 957 had failed multiple PI containing regimens.

Comment: A statement was inserted to clarify that the NNRTI naïve patients in Study 957 received efavirenz.

Comment: Data in the last two paragraphs were inserted into table format for ease of use.

CONCLUSIONS

The sponsor has accepted the proposed changes to the Microbiology section of the label.

Julian J. O'Rear, Ph.D.
Microbiologist

CONCURRENCES

Date: _____
HFD-530/Assoc Dir/J Farrelly

Date: _____
HFD-530/Acting TL Micro/Julian J. O'Rear

cc:
HFD-530/Original IND
HFD-530/Division File
HFD-530/Reviewer Medical/Struble
HFD-530/RPM/Belouin

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

/s/

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1/17/02 02:37:46 PM
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