

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-906

CHEMISTRY REVIEW(S)

NDA 21-906

KALETRA[®]
(lopinavir/ritonavir)
Film-Coated Tablets

200 mg/50 mg

Abbott Laboratories

Ko-Yu Lo, Ph.D.
Division of Antiviral Drug Products



Table of Contents

Table of Contents.....	2
Chemistry Review Data Sheet.....	3
The Executive Summary.....	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block.....	11
Chemistry Assessment.....	12
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	12
S DRUG SUBSTANCE [Name, Manufacturer].....	12
P DRUG PRODUCT [Name, Dosage form].....	12
A APPENDICES.....	52
R REGIONAL INFORMATION.....	52
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	52
A. Labeling & Package Insert.....	Error! Bookmark not defined.
B. Environmental Assessment Or Claim Of Categorical Exclusion.....	53
III. List Of Deficiencies To Be Communicated.....	54



Chemistry Review Data Sheet

1. NDA # 21-906
2. REVIEW #: 1
3. REVIEW DATE: 10/27/2005
4. REVIEWER: Ko-Yu Lo, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

29/APR/2005

Amendment BC

26/SEP/2005

Amendment IN

21/OCT/2005

Amendment UX

25/OCT/2005

Amendment IN

26/OCT/2005

7. NAME & ADDRESS OF APPLICANT:

Name: Abbott Laboratories

Address: 200 Abbott Park Road, RA76, AP30-1NE
Abbott Park, IL 60064-6157Representative: Mary Ellen Snyder, Associate Director
Global Pharmaceutical Regulatory Affairs

Telephone: 847-937-9977



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: KALETRA®
- b) Non-Proprietary Name (USAN): Lopinavir/Ritonavir
- c) Code Name/# (ONDC only): LPV/RTV
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Film-coated tablet

12. STRENGTH/POTENCY: 200 mg/50 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

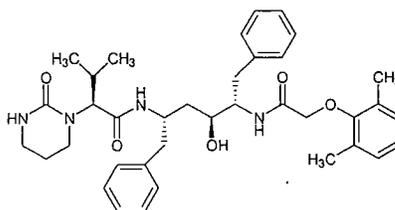
Lopinavir

[1S-[1R*, (R*),3R*,4R*]]-N-[4-[[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide

CAS Registry Number 192725-17-0

Formula C₃₇H₄₈N₄O₅

M.W. 628.80



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*)]-

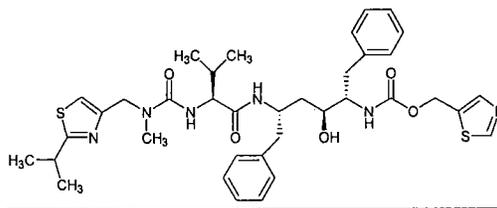
CAS Registry Number 155213-67-5

Formula C₃₇H₄₈N₆O₅S₂

M.W. 720.95



Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:****A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	III	[Redacted]	[Redacted]	4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			3	Adequate		
	III			1	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	51,715	Kaletra Tablets

18. STATUS:**ONDC:**

	RECOMMENDATION	DATE	REVIEWER



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Biometrics	N/A		
EES	Acceptable	10/25/05	HFD-322
Pharm/Tox	Acceptable (Impurity and excipient)	10/27/05	James Farrelly
Biopharm	Dissolution Specification Acceptable	10/27/05	Derek Zhang & Ko-Yu Lo
LNC	N/A		
Methods Validation	Not Sent		
OPDRA	Acceptable		
EA	Exclusion Acceptable	10/27/05	Ko-Yu Lo
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-906

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. Co-formulated KALETRA products are currently marketed as KALETRA Soft Gelatin Capsules (133.3 mg/33.3 mg) and KALETRA Oral Solution (80 mg/20 mg).

Drug Substance

CMC information for the active pharmaceutical ingredient, lopinavir (LPV) and the pharmacokinetic enhancer, ritonavir (RTV) is cross referenced to the approved NDA 21-226 for Kaletra Capsules and NDA 20-659 for Norvir (ritonavir) Oral Solution. Both LPV and RTV are BCS class IV compounds (low solubility and low permeability).

RTV have been isolated. Although the two compounds are poorly soluble, the particle size distribution and crystal form will not have a significant impact on the dissolution or bioavailability of the proposed tablet dosage form since LPV and RTV are dissolved in a solution for tableting.

Drug Product

KALETRA Tablets is an immediate release film coated tablets containing 200 mg lopinaivr and 50 mg of ritonavir. This tablet dosage form has the following advantages:



Chemistry Assessment Section

(i) it has a higher drug loading (200 mg/50 mg) than the current soft gelatin capsule (133.3 mg/33.3 mg) which reduces the daily "pill burden" from 6 to 4 units daily; (ii) it is stable at room temperature throughout shelf-life while the approved capsule and oral solution dosage forms require storage under refrigeration. Room temperature stability of the tablet dosage form provides worldwide patient accessibility as well as patient convenience, and (iii) it has a more consistent pharmacokinetic behavior and a reduced food effect compared to the capsule dosage form. The high drug loading and room temperature stability of the tablet formulation was achieved using solid dispersion technology. LPV and RTV are dissolved in a polymer/surfactant matrix via a

Key Attributes of the KALETRA Tablets Formulation

2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process



Chemistry Assessment Section

B. Description of How the Drug Product is Intended to be Used

KALETRA Tablets is indicated in combination with other antiretroviral agents for the treatment of HIV-infection.

The recommended dose of Kaletra tablets is 400 mg/100 mg (2 tablets) twice-daily with or without food. Kaletra Tablets are packaged in hi_ [redacted] bottles as 120 counts per bottle. To inform patients about avoiding exposure of Kaletra tablets to high humidity over an extended period of days the following labeling statement will be included in the container label, packet insert and patient packet insert:

[redacted]

A 24 months expiration dating period is approved based on [redacted] long-term stability data at 25°C/60%RH for commercial-scale batches using [redacted] and 24 months long-term stability data for one pilot-scale batch.

C. Basis for Approvability or Not-Approval Recommendation

After pre-approval inspection, all manufacturing and testing facilities were found acceptable.

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for the product of KALETRA (lopinavir/ritonavir) Tablets, 200 mg/50 mg

III. Administrative

A. Reviewer's Signature

Chemist:

Ko-Yu Lo, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

ChemistryTeamLeader

Stephen P. Miller, Ph.D. {Signed Electronically in DFS}

C. CC Block

HFD-830 Division Director (Acting)

Norman Schmuft, Ph.D.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21906/000

Sponsor: ABBOTT LABS

Org Code : 530

NO CITY, , XX

Priority : 3P

Brand Name : KALETRA TABLETS

Stamp Date : 29-APR-2005

Estab. Name:

PDUFA Date : 29-OCT-2005

Generic Name: LOPINAVIR TABLETS

Action Goal :

Dosage Form: (TABLET)

District Goal: 30-AUG-2005

Strength : 200/50 MG

FDA Contacts:	V. REDDY	Project Manager	301
-796-0793			
	K. LO	Review Chemist	301
-796-1982			
	S. MILLER	Team Leader	301
-796-1418			

Overall Recommendation: ACCEPTABLE on 25-OCT-2005 by S. ADAMS (HFD-322)
301-827-9051

Establishment : CFN : 9610142 FEI : 3002807401
ABBOTT GMBH AND CO KG
KNOLLSTRASSE
LUDWIGSHAFEN AM RHEIN, , GM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-OCT-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1411365 FEI : 1411365
ABBOTT LABORATORIES
1401 14TH AND SHERIDAN RD
NORTH CHICAGO, IL 60064

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-JUL-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1415939 FEI : 1415939
ABBOTT LABORATORIES
100/200 ABBOTT PARK RD
ABBOTT PARK, IL 60064

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-MAY-05
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9611151 FEI : 3002806277
ABBOTT SPA
KM 52-04010
CAMPOVERDE, LATINA, IT

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-OCT-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

58 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-

2