# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# NDA 21-814

# Chemistry Review(s)

# ESTABLISHMENT EVALUATION REQUEST

## SUMMARY REPORT

Application : NDA 21814/000
Org Code : 530
Priority : 1P

Sponsor: BOEHRINGER PHARMS
900 RIDGEBURY RD
RIDGEFIELD, CT 06877

Stamp Date : 22-OCT-2004
PDUFA Date : 22-JUN-2005
Action Goal :
District Goal: 23-APR-2005

Brand Name : APTIVUS (TIPRANAVIR) 250MG
CAPSULES
Estab. Name:
Generic Name: TIPRANAVIR
Dosage Form: (CAPSULE)
Strength : 250 MG

FDA Contacts: T. SINHA Project Manager (HFD-530) 301-827-2368
K. LO Review Chemist (HFD-530) 301-827-2397
S. MILLER Team Leader (HFD-530) 301-827-2392

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Overall Recommendation: ACCEPTABLE on 02-MAY-2005by J. D AMBROGIO(HFD-322) 301-827-9049

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Establishment : CFN : 9610492 FEI : 3002806556
BOEHRINGER INGELHEIM KG
INGELHEIM AM RHEIN, , GM

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JAN-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : [redacted] FEI : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-JAN-05

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

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Establishment : CFN : [redacted] FEI : [redacted]

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: [redacted]

Profile : CSG OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-FEB-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : [redacted] FEI : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSG OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-MAY-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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Establishment : CFN : [redacted] FEI : [redacted]

DMF No: AADA:

Responsibilities: [ ]

[ ]

[ ]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-JAN-05

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

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# NDA 21-814

## APTIVUS®
## (tipranavir)
## Capsule

## 250 mg

**Boehringer Ingelheim Pharmaceuticals, Inc.**

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

# Table of Contents

# Chemistry Review Data Sheet

1. NDA # 21-814

2. REVIEW #: 1

3. REVIEW DATE: 6/21/2005

4. REVIEWER: Ko-Yu Lo, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original | 22/DEC/2004 |
| Amendment BC | 21/MAR/2005 |
| Amendment BC | 24/MAR/2005 |
| Amendment BC | 25/MAR/2005 |
| Amendment BC | 24/MAY/2005 |
| Amendment BC | 27/MAY/2005 |
| Amendment BC | |
| Amendment BC | |

7. NAME & ADDRESS OF APPLICANT:


| | |
|---|---|
| Name: | Boehringer Ingelheim Pharmaceuticals, Inc. |
| Address: | 900 Ridgebury Road, P.O. Box 368<br>Ridgefield, CT 06877 |
| Representative: | Nancy S. McKay, P.E., Sr. Associate Director<br>Drug Regulatory Affairs |
| Telephone: | 203-791-6759 |

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: APTIVUS®
b) Non-Proprietary Name (USAN): Tipranavir
c) Code Name/# (ONDC only): TPV
d) Chem. Type/Submission Priority (ONDC only):

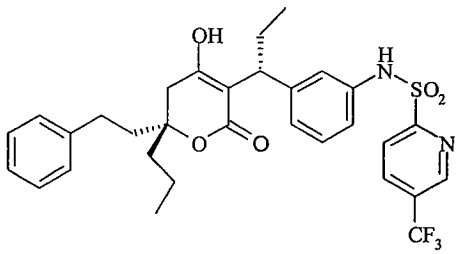
- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Antiviral
11. DOSAGE FORM: Capsule (soft gelatin)
12. STRENGTH/POTENCY: 250 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:

USAN: 3'-[(1R)-1-[(6R)-5,6 dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2H-pyran-3-yl]propyl]-5-(trifluoromethyl)-2-pyridinesulfonanilide
IUPAC 2-Pyridinesulfonamide, N-[3-[(1R)-1-[(6R)-5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)
CAS Reg. No. 174484-41-4
Synonym: PNU-140690
Molecular Formula $C_{31}H_{33}F_3N_2O_5S$
Molecular Weight 602.7
Structure Formula



Chemistry Review Data Sheet

## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | Tipranavir capsules | 1 | Adequate* | 6/21/2005 | Per agreement with the applicant, an executed batch record for the drug product is provided in the DMF. |
| | III | | | 3 | Adequate | | |
| | III | | | 3 | Adequate | | |
| | III | | | 3 | Adequate | | |
| | III | | | 3 | 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 | 51,979 | Tipranavir Capsules |

## 18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|

Chemistry Review Data Sheet

| | | | |
|---|---|---|---|
| Biometrics | N/A | | |
| EES | Acceptable | 5/2/2005 | HFD-322 |
| Pharm/Tox | Acceptable (Impurity and excipient) | 6/21/2005 | Anita Bigger |
| Biopharm | Dissolution Specification Acceptable | 6/21/2005 | Derek Zhang & Ko-Yu Lo |
| LNC | N/A | | |
| Methods Validation | Not Sent | | |
| OPDRA | Acceptable | | |
| EA | Exclusion Acceptable | 6/21/2005 | 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 21-814

## *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)

The drug substance, tipranavir (TPV) is a protease inhibitor of human immunodeficiency virus (HIV) belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides. The following two physicochemical and biopharmaceutical properties of TPV have played critical role in the formulation development and treatment regimen: (a) TPV is a BCS Class IV (low solubility-low permeability) compound, and (b) TPV is very rapidly metabolized. The extremely low aqueous solubility but high lipophilicity of TPV leads to the development of a soft gelatin capsule dosage form containing a fill formulation [ ] to overcome the dissolution rate limited absorption of TPV. TPV is primarily metabolized in the liver by CYP 450 3A4. Co-administration of TPV with low-dose ritonavir (a CYP 3A inhibitor) greatly enhances the bioavailability of TPV.

Tipranavir is a chiral synthetic compound with the 1R, 6R configuration. It is synthesized by [ ] Designation of [ ] qualification of supplier(s) have been discussed and agreed upon during the pre-NDA meeting. The commercial manufacturing process [ ] as well as controls [ ] drug substance is acceptable. Critical controls for the [ ] are identified as specific tests for [ ] Per request, [ ] was later amended as a critical operation parameter for maintaining low impurity levels in the drug substance (DS).

Executive Summary Section

The structure of TPV has been established [ ] Impurity profile of [ ] drug substance has been established based on the actual [ ] drug substance at release and actual degradation products observed in the primary stability samples. A reference standard has been prepared. An extensive [ ]

] The physicochemical properties [ ]

]

TPV drug substance produced by [ ] is a white to off-white to slightly yellow solid. Specification for the DS includes [ ]

]

Acceptance criteria for the DS specification is determined using a mean + 3 σ approach based on release data from ~ commercial-scale batches, stability data at 25°C/60%RH for ~ months and the impurity qualification levels obtained from animal toxicology studies. The revised DS specification is acceptable.

Degradation pathways of TPV have been established by stress studies. In solid state, TPV mainly undergoes oxidative degradation, whereas in aqueous solution, TPV undergoes both hydrolysis (major degradation pathway) and oxidation. TPV is not sensitive to light irradiation. Stability of the DS has been evaluated on 3 commercial-scale [ ] lots at long-term conditions (25°C/60% RH), intermediate conditions (30°C/70%RH) and accelerated conditions (40°C/75%RH). The long-term stability data support a ~ month retest period.

The drug product, APTIVUS® Capsules 250 mg is a soft gelatin capsule. Pharmaceutical development studies have been performed to ensure that the proposed capsule fill formulation meets the following criteria: TPV solubility in the individual excipient and in final vehicle, TPV physical and chemical stability in the vehicle, fill vehicle dispersibility in an aqueous medium, TPV bioavailability as delivered from the vehicle, and vehicle compatibility with gelatin and components of the gelatin formulation. APTIVUS capsules are manufactured by contractor [ ]

]

]. Critical steps in the manufacture are identified and in-process controls and testing procedures are established. Specification of the drug product includes:

]

Stability data were generated from — ommercial-scale lots for up to — months at 25°C/60%RH, 12 months at 30°C/70%RH, and 6 months at 40°C/75%RH. All test parameters show no significant changes at 25°C/60%RH, and 30°C/70%RH except the tris content in the capsule fill was found to decrease from — at release to — at — months at 25°C/ 60%RH due to interaction with fatty acid component of excipients and with TPV degradation product. Tris is an excipient [

]

Data submitted in the original NDA demonstrate the dissolution/dispersion of TPV capsule in — minutes is approximately — and the dissolution profile does not [ — When the — content is reduced below — the extent of dispersion is greatly decreased ([ ] — Additional studies were conducted to evaluate the excipient composition variation on droplet size distribution of dispersed globules (Amendment N044). The data show the [ ] Dispersion of the fill solution in aqueous media produced [ ] emulsion with a majority of the droplets less than — All available data demonstrate the *in vitro* performance of TPV capsules remain the same for —months at 25°C/ 60%RH. .

Decrease of — Content at [ ] Storage and Related Regulatory Impact

During the NDA review, a European chemistry reviewer asked BI to provide information to support the bioavailability of the product at the end of shelf-life, specifically with respect to the [ ] Since human bioavailability data on TPV capsule with low — content was not available at this time, the applicant submitted an amendment (N041) to change the storage condition from — to refrigeration based on better stability of — at [ ] ambient RH and the fact that all the clinical lots were stored at refrigeration. The applicant plans to conduct a bioavailability study comparing TPV capsules with — and — to support a future supplement for — storage.

Due to the storage condition change, the following CMC sections are affected and reevaluated: Specification for drug product, analytical procedures for degradation products, justification of specifications, stability summary and conclusions, post-approval stability protocol, and stability data at — ambient RH.

Acceptance criteria of the drug product are determined using a mean + 3 σ approach based on release data from the — batches used for pivotal clinical trials and primary

stability studies and the [ ] stability data at — ambient RH. The revised DP specification is acceptable..

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

APTIVUS (tipranavir), co-administered with [ ] ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

The recommended dose of APTIVUS (tipranavir) Capsules is 500 mg (two 250 mg capsules), co-administered with 200 mg ritonavir (low-dose ritonavir), twice daily.

APTIVUS Capsules are packaged in high-density polyethylene (HDPE) bottles as 120 counts per bottle. The bottles are stored in a refrigerator (2-8°C; 36-46°F) prior to opening the bottle. After opening the bottle, the capsules may be stored at 25°C (77°F), with excursions permitted to 15°-30°C (59-86°F) and must be used within 60 days.

A 36 months expiration dating period is approved based on [ ] long-term stability data at — ambient RH for — commercial-scale batches using linear regression analysis and a [ ] lower prediction interval approach.

## 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 APTIVUS® Capsules, 250 mg.

The following issues have been raised and resolved during the NDA review:

(1) Acceptance criteria for the impurities [ ] were revised to be consistent with FDA assessment of toxicological qualification and manufacturing capability (mean + 3 σ).
(2) The storage condition was changed from — to refrigeration.
(3) The dissolution acceptance criteria was revised to Q=[ ] in — minutes.
(4) [ ] was identified as a critical operation parameter [ ] of the drug substance manufacturing process.
(5) [ ] of the drug substance was limited to [ ] batch and included in the description of the manufacturing procedure.

The Quality Overall Summary (QOS) adopts the same format as Module 3. Each CMC section for the drug substance and drug product contains pertinent information. When applicable, provides rationale and discussion. However, in spite of a relatively comprehensive summary, the reviewer needs to evaluate the data submitted in the Module 3 to validate whether the study results/conclusions reported in the QOS is correct, specifically, on sections for DS structure and characterization, DS manufacture, impurity qualification, DS specification, pharmaceutical development, excipient selection and qualification, DP specification, stability data and analysis, and analytical procedure validations. In the case of this NDA, issues cited above cannot be identified by the evaluation of the QOS.

## 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 Schmuff, Ph.D.

60 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Ko-yu Lo
6/22/05 11:03:40 AM
CHEMIST

Stephen Paul Miller
6/22/05 11:32:14 AM
CHEMIST