

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-814s005/22-292

CHEMISTRY REVIEW(S)



Chemistry Assessment Section

NDA 21-822

NDA 22-292

APTIVUS[®]
(tipranavir)
Oral Solution

100 mg/mL

Boehringer Ingelheim Pharmaceuticals, Inc.

Ko-Yu Lo, Ph.D.

Branch IV

Division of Pre-Marketing Assessment 2

Office of New Drug Quality Assessment



Chemistry Review Data Sheet

1. NDA # 21-822, 22-292
2. REVIEW #: 2
3. REVIEW DATE: 6/19//2008
4. REVIEWER: Ko-Yu Lo, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

CMC Review #1

Document Date

6/21/2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment AZ

Amendment BC

Document Date

12/20/2007

03/18/2008

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Address: Boehringer Ingelheim Pharmaceuticals, Inc.

Representative: 900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877Telephone: Charles R. Mazarella , Associate Director
Drug Regulatory Affairs

203-791-5462

Chemistry Assessment Section

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: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 100 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

 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-pyridinesulfonamide

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)

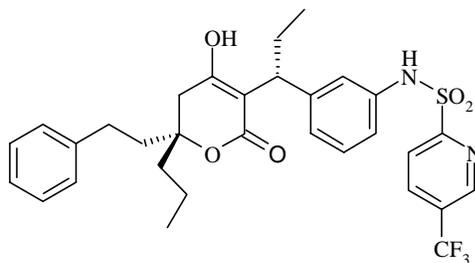
CAS Reg. No. 174484-41-4

Synonym: PNU-140690

Molecular Formula $C_{31}H_{33}F_3N_2O_5S$

Molecular Weight 602.7

Structure Formula



The Chemistry Review for NDAs 21-822 & 22-292

Background

NDA 21-822 was recommended for approval in 2005 from a CMC standpoint (see Chemistry Review #1). The NDA received an AE action due to clinical deficiencies. Per agreement, the firm now provides updated release and stability data in the resubmission to ensure the chemical stability (b) (4) and physical stability (b) (4) of the drug product.

This Chemistry Review#2 addresses the CMC information update and labeling submitted in the resubmission.

Recommendation and Conclusion

From chemistry, manufacturing, and controls (CMC) standpoint, NDA 21-822 and NDA 22-292 are recommended for Approval.

CMC Information Update Acceptable

1. Batch Analysis on 13 batches (clinical and stability) of TPV Oral Solution 100 mg/mL
 - (i) (b) (4)
 - (ii) Degradation products -- All 13 batches showed no degradation products above the ICH Q3B (R2) reporting threshold of (b) (4). Therefore, per ICH guideline, there are no reportable results for individual or total degradation product at release.
 - (iii) All 13 batches met the ACs of the DP specification (see Review #1).

Comment: The release data support the DP specification established in Review #1.

2. Stability Update

Stability studies were conducted on 8 batches of TPV Oral Solution 100 mg/mL at long-term (25°C/60%RH), intermediate (30°C/70%RH) and accelerated (40°C/75%RH) conditions (b) (4) and photosensitivity studies are conducted in one stability lot. Up to 36 months data at long term (25°C/60%RH), 12 months data at intermediate (30°C/70%RH) and 6 months data at accelerated (40°C/75%RH) are reported. The study results indicated that TPV is chemically stable in the drug product over the study periods: No significant loss in TPV concentration, and no degradation products were detected at levels above (b) (4)

Chemistry Assessment Section

Table 3 Accuracy of dose volume delivery of Tipranavir oral solution by a dosing syringe

Syringe		Nominal Dose Volume (mL)			
		0.8	1.2	2.5	5
1	Average (mL)	0.81	1.18	2.45	4.85
	Absolute difference from NV (mL)	0.0095	-0.0178	-0.0502	-0.1461
	% Difference from Nominal Volume	1.19	-1.48	-2.01	-2.92
2	Average (mL)	0.78	1.19	2.45	4.83
	Absolute difference from NV (mL)	-0.0166	-0.0125	-0.0503	-0.1727
	% Difference from Nominal Volume	-2.08	-1.04	-2.01	-3.45
3	Average (mL)	0.80	1.17	2.43	4.86
	Absolute difference from NV (mL)	-0.0041	-0.0253	-0.0661	-0.1390
	% Difference from Nominal Volume	-0.51	-2.11	-2.64	-2.78
4	Average (mL)	0.80	1.19	2.44	4.86
	Absolute difference from NV (mL)	-0.0039	-0.0089	-0.0585	-0.1399
	% Difference from Nominal Volume	-0.49	-0.74	-2.34	-2.80

Comment: The submitted data demonstrate that the dosing syringe provides an accurate and reproducible means of administering the TPV Oral Solution. Acceptable

Labeling

- a) Container Label Acceptable



1 pp withheld in full immediately after this page as (b)(4) Draft labeling

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

/s/

Ko-yu Lo
6/20/2008 03:54:27 PM
CHEMIST

Stephen Paul Miller
6/20/2008 04:52:08 PM
CHEMIST
NDAs 21-822 and 22-292 are recommended for approval from
the CMC perspective