CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-822

CHEMISTRY REVIEW(S)

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	Document Date
CMC Review #1	6/21/2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AZ	12/20/2007
Amendment BC	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 06877
Telephone:	Charles R. Mazzarella , Associate Director Drug Regulatory Affairs
	203-791-5462

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: _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)

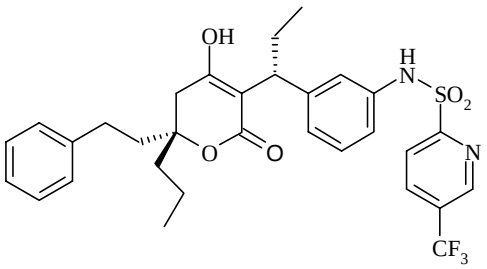
CAS Reg. No. 174484-41-4

Synonym: PNU-140690

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

Molecular Weight 602.7

Structure Formula



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 (b) (4) 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)

(4)

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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

(b) (4)

[redacted]

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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