

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-187

CHEMISTRY REVIEW(S)

NDA 22-187

**Intelence[™]
(etravirine)
Tablets**

Tibotec, Inc.

**Sharmista Chatterjee, Ph.D.
Mark R. Seggel**

CMC Review Team

**Office of New Drug Quality Assessment
for
Division of Antiviral Products**

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Chemistry Review Data Sheet

1. NDA 22-187
2. REVIEW #: 1
3. REVIEW DATE: 07-JAN-2008
4. REVIEWER: Sharmista Chatterjee, Ph.D.
Mark R. Seggel
5. PREVIOUS DOCUMENTS:

Previous Documents

Not Applicable

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Pre-submission

Resubmission

Original Application

SU

BC

BC

Document Date

04-JUN-2007

06-JUL-2007

17-JUL-2007

04-OCT-2007

31-OCT-2007

14-DEC-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Tibotec, Inc.
Address:	1020 Stony Hill Road, Suite 300 Yardley, PA 19067
Representative(s):	Susan Fiordeliso, Manager, Global Regulatory Affairs
Telephone:	609-730-7500

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8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Intelence™
- b) Non-Proprietary Name (USAN): etravirine (e" tra v|r' een)
- c) Code Name/#: TMC125 (R165335, JNJ-4371315)
- d) CAS Registry Number: 269055-15-4
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 1
 - ii. Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)

10. PHARMACOL. CATEGORY: Antiviral (HIV), NNRTI

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

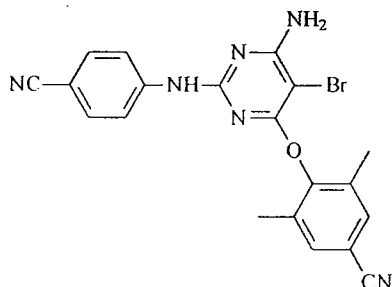
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

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

Chemical Name: 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile



Molecular Formula: C₂₀H₁₅BrN₆O

Molecular Weight: 435.28

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17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
20440	II	Janssen	Drug Substance	1	Adequate	07-JAN-2008	
/	III			4			
/	III			4			
/	III			4			
/	III			4			
/	III			4			
/	III			4			
/	III			4			
/	III			4			

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
Investigational New Drug Application	IND 63,646	TMC125 for HIV

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable		
EES	Acceptable	07-JAN-2008	S.Adams, HFD-322
Pharm/Tox	Impurity qualification acceptable	20-DEC-2007	KMWu, HFD-530
Biopharm	Not applicable		
LNC	Not applicable		
Methods Validation	Not applicable		
DMETS	Trademark acceptable; other	07-DEC-2007	Denise Toyer

CHEMISTRY REVIEW**Chemistry Review Data Sheet**

	comments provided		
EA	Categorical exclusion acceptable	20-DEC-2007	M. Seggel
Microbiology	Not applicable		

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for NDA 22-187

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

As amended, this New Drug Application for Intelence™ (etravirine) Tablets, 100-mg, is recommended for approval from the Chemistry, Manufacturing and Controls perspective.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

Etravirine (TMC125) is a synthetic non-nucleoside inhibitor of HIV-1 reverse transcriptase. The chemistry, manufacturing and controls for etravirine are documented in Type II DMF 20440, held by Janssen Pharmaceutica (a subsidiary, as is Tibotec, of J&J).

Etravirine is obtained as a _____ with very low aqueous solubility across a wide range of pH. It also has relatively low permeability _____. Etravirine has a pKa _____ and logP (octanol-pH 7 buffer partition coefficient) _____. These properties directly affected drug product formulation development.

Critical quality attributes of the drug substance including identification, assay, and purity. Drug substance _____ and particle size are considered non-critical physicochemical properties because the _____.

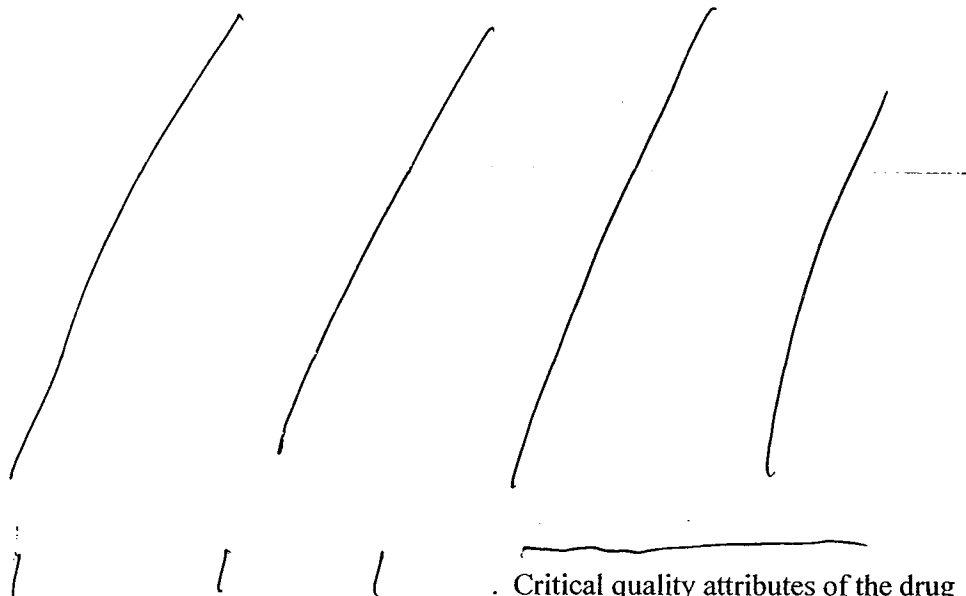
The drug substance is relatively stable; no extraordinary storage precautions are required other than standard protection from moisture and light.

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(2) Drug Product

The drug product is supplied as white to off-white, oval tablets containing 100 mg of etravirine for oral administration. Each tablet is embossed with "TMC125" on one side and "100" on the other side. Inactive ingredients include: hypromellose, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and lactose monohydrate.

To improve the apparent solubility (and hence bioavailability) of etravirine, a formulation was developed. In this system,



Critical quality attributes of the drug product include identification, assay, purity and dissolution.

The drug product is packaged in bottles with child-resistant PP closures and induction innerseals. Three desiccant pouches are included in the bottles to limit moisture.

The stability of the and drug product has been demonstrated under ICH conditions.

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

The recommend oral dose in adults is 200 mg (two 100 mg tablets) taken twice daily following a meal. The product is supplied in bottles of 120. The tablets are to be stored in the original bottle, which includes three desiccant pouches to provide protection from moisture. The pouches are not to be removed or eaten. The drug product is to be stored at 25°C (with excursions permitted to 15°-30°C) [USP

Executive Summary Section

controlled room temperature]. The proposed expiration dating period of 24-months when stored as directed is supported by stability data.

C. Basis for Approvability or Not-Approval Recommendation

The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant.

Drug substance chemistry, manufacturing and controls are adequately documented in DMF 20440. Note that toxicological qualification of potential drug substance impurities was documented in the NDA pharm/tox section. Based on review of this material, Dr. K.M. Wu, DAVP, concurred with the applicant's assessment. Impurities in the drug substance are thus adequately controlled.

Review of the drug product information resulted in several comments for the applicant. These primarily related to the spray-dried powder and tablet manufacturing processes. The applicant's responses to the comments have been found to be adequate.

Drug product (and drug substance) specifications provide assurance of the identity, strength, quality, purity and bioavailability of the product. Validation of the analytical procedures has been adequately documented. Verification of the procedures, which involve commonly used techniques, by FDA laboratories is not needed.

All drug substance and drug product manufacturing, packaging and control facilities were submitted to EES. The tablet manufacturing facility (Latina, Italy) was inspected; no 483 observations were reported. However, a 483 was issued following inspection of the Geel, Belgium drug substance and spray-dried powder manufacturing facility. An overall recommendation of Acceptable was issued by the Office of Compliance on 07-JAN-2008.

III. Administrative**A. Reviewer's Signature**

{see electronic signature page}

B. Endorsement Block

{see electronic signature page}

C. CC Block

{see dfs}

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/s/

Mark Seggel
1/14/2008 02:20:44 PM
CHEMIST

Norman Schmuff
1/14/2008 02:30:23 PM
CHEMIST

MEMORANDUM

Date: January 9, 2008

To: NDA 22-187

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-187 Intelence (Etravirine)
Tablets from applicant Tibotec, Inc

I have assessed the ONDQA review of NDA 22-187. I concur with the approval recommendation from a CMC perspective.

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/s/

Elaine Morefield
1/9/2008 11:10:56 AM
CHEMIST