CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-976

CHEMISTRY REVIEW(S)

NDA #21-976

PREZISTA™
(darunavir)
Tablets
300 mg

Tibotec, Inc.

CMC Review
Rao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist
ONDQA, DPA II, Branch IV

Chemistry Review Data Sheet

1. NDA# **21-976**

2. REVIEW #: 1

3. REVIEW DATE: 6/23/2006

4. REVIEWER: Rao V. Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Pre-submission RRZ 002	4/Nov/2005
Original N 000	22/Dec/2005
Amendment N 000 BC	27/Feb/2006
Amendment N 000 BL	1/Jun/2006
Amendment N 000 BC	19/Jun/2006
Amendment N 000	21/Jun/2006
Amendment N 000 BL	22/Jun/2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Tibotec, Inc.
Address:	1020 Stony Hill Road, Ste 300 Yardley, PA 19067
Representative:	Jenny Z. Lin, Pharm. D. Manager, Regulatory Affairs
Telephone:	609-730-7516

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: PREZISTA™
b) Non-Proprietary Name (USAN): darunavir
c) Code Name/#: TMC 114, TMC 114 ethanolate, TMC 114 monoethanolate, R319064, JNJ-25875382, darunavir ethanolate.
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1

- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL CATEGORY: Antiviral (protease inhibitor)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 300 mg (each tablet contains darunavir ethanolate equivalent to 300 mg of the free form of darunavir)

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:

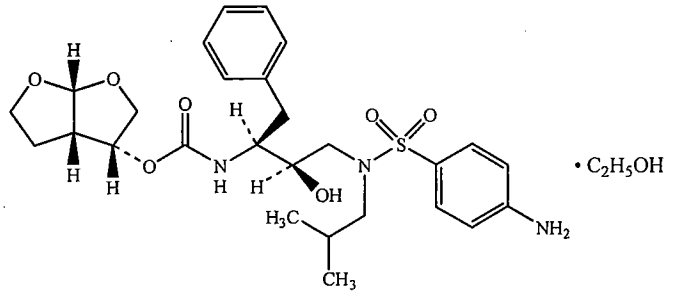
Chemical Name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate

CAS Reg. No.: N/A (206361-99-1 for free darunavir)

Molecular Formula: $C_{27}H_{37}N_3O_7S \cdot C_2H_5OH$

Molecular Weight: [redacted]

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
[redacted]				Adequate
				Adequate
				Adequate
				Adequate
				Adequate
				Adequate
				Adequate
				Adequate

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,477	TMC 114 (darunavir) Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable	3/29/06	J.D. Ambrogio (HFD-322), DMPQ, OC
Trademark Review	Acceptable	4/7/06	DMETS (HFD-420), ODS
EA	Acceptable (Categorical Exclusion)	6/21/06	Rao Kambhampati, Ph.D.
Biopharm for Dissolution Method including acceptance criteria	Acceptable	6/21/06	Vikram Arya, Ph.D.
Methods Validation	Not necessary	6/21/06	Rao Kambhampati, Ph.D.

The Chemistry Review for NDA 21-976

The Executive Summary

I. Recommendations

- **A. Recommendation and Conclusion on Approvability**
  From the chemistry, manufacturing and controls (CMC) standpoint, the NDA #21-976 is recommended for approval.

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

II. Summary of Chemistry Assessments

- **A. Description of the Drug Substance(s) and Drug Product(s)**
  The Applicant intends to seek approval of the FDA for PREZISTA™ (darunavir) Tablets for co-administration with 100 mg of ritonavir, and with other active antiretroviral agents for the treatment of HIV infection in antiretroviral treatment-experienced adult patients. Each Prezista (darunavir) tablet contains darunavir ethanolate ( ) equivalent to 300 mg of the free form of darunavir. The tablets are orange, oval-shaped, film-coated, and debossed with "300" on one side and "TMC114" on the other side. The tablets are packaged in 160-mL bottles of 120 count.

  All information regarding the chemistry, manufacturing and controls (CMC) for darunavir drug substance was cross-referenced to the Janssen Pharmaceutica NV's and a Letter of Authorization (LOA) was submitted to the NDA. The DMF and its amendments there to, contained adequate CMC information for darunavir drug substance.

  The drug product is a film-coated tablet. The total weight of each tablet is 650.20 mg. The core of each tablet contains of darunavir ethanolate which is equivalent to 300 mg of free darunavir as the active ingredient and the following excipients, microcrystalline cellulose and colloidal silicon dioxide) , crospovidone and magnesium stearate The film-coating contains Opadry II Orange The commercial darunavir tablets are manufactured by Janssen Ortho L.L.C., Gurabo (Puerto Rico). The secondary packaging is performed by Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ. The stability testing of the marketed product will be performed by Janssen Pharmaceutica Inc., Titusville, NJ. Tibotec and all these companies are the affiliated companies of Johnson & Johnson. The initially intended commercial batch size was kg but it was later revised to The primary stability data were provided for registration batches of each. The manufacturing process involves the following steps:

[redacted] The in-process controls included adequate tests and acceptance criteria. The tablet release specifications included [redacted] HPLC), assay ([redacted], chromatographic purity (each individual degradation product NMT [redacted] and Total degradation products NMT [redacted], weight variation (USP <905>), and dissolution (NLT [redacted] of darunavir [redacted]. Upon comment, in the amendment (6/19/06) the Total degradation products content was tightened from initial [redacted] Adequate description was provided for the analytical methods [redacted] and dissolution). The method validation was conducted on [redacted] which is acceptable because this change does not affect the test results. Batch analyses data were provided for [redacted] NDA registration batches ([redacted] kg) that were manufactured at the proposed commercial site (Janssen-Ortho, Gurabo, PR) and for [redacted] batches that were manufactured at Johnson & Johnson Pharmaceutical Research and Development (J&JPRD) at Spring House, PA. In addition, upon comment, batch analyses data were provided in the amendment (6/19/06) for [redacted] full production scale [redacted] batches that were made at Gurabo which also included [redacted] process validation batches. It was demonstrated that the darunavir tablets can be made with consistent quality and purity. The container/closure system consists of [redacted] However, the 120 count bottles will only be marketed at this point. Adequate description, specifications, and test results were provided for container/closure components. The initial submission (11/4/05) contained [redacted] months of long term and accelerated stability data for [redacted] primary stability batches. The [redacted] long-term updated data were provided in the NDA amendment (2/27/06). In addition, in the initial submission, [redacted] long-term and [redacted] accelerated supportive stability data were provided for one batch each of the 300 mg and 400 mg strength tablets which was followed by [redacted] long-term updated data in the 2/27/06 amendment. Based on the real time stability data and statistical analysis of the data, the applicant proposed an expiration dating period of 18 months when darunavir tablets are stored at 25°-30°C.

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

The PREZISTA™ (darunavir) tablets are administered orally. The recommended dose for adults is 600 mg (two 300 mg tablets) twice daily taken with ritonavir 100 mg twice daily and with food. Ritonavir is used as a pharmacokinetic enhancer of Prezista. The tablets are packaged in 160-mL [redacted] bottles of 120 count. The tablets are recommended to be stored at 25°C (77°F); with excursions permitted to 15° to 30°C (59° to 86°F). The expiration dating period is [redacted] when stored at 25°-30°C (59°-86°F).

- **C. Basis for Approvability or Not-Approval Recommendation**

The original NDA submission and amendments there to, provided adequate information on the chemistry, manufacturing, and controls (CMC) for the production of PREZISTA

(darunavir) tablets. The DMF [redacted] and amendments there to found to contain adequate CMC information for darunavir drug substance.

The manufacturing and packaging processes and in-process controls used for the drug product are acceptable. Adequate batch analysis data were provided for the drug product which included data for full production scale and [redacted] process validation batches. The specification for the drug product included adequate tests, and the revised acceptance criteria are acceptable. The stability data included [redacted] ; real-time long-term stability data for [redacted] primary registration batches and [redacted] long-term data for one supportive stability batch and, and statistical analysis which projected an expiration period of [redacted] months for 120-count bottles. On the basis of the real time data and statistical analysis of the data, the proposed expiration dating period of 18 months is acceptable when tablets are stored at 25°-30°C.

The trade name, PREZISTA™, was found to be acceptable by the DMETS (HFD-420), DDMAC, and DAVP (HFD-530). The established (USAN) name for the drug substance is darunavir. Some changes were recommended to the package insert and bottle and carton labels and those changes will be incorporated in the final printed labeling documents by the Applicant.

The manufacturing, packaging, and release testing facility and the commercial stability testing facility for darunavir tablets were found to be acceptable by DMPQ (HFD-324). The dissolution method including the acceptance criteria is acceptable from the CMC and from the biopharm perspective (Vikram Arya, Ph.D.). As according to the current policy, the analytical methods validation is not required because the dosage form is simple and it does not involve any unusual/special testing methods. The Applicant's request for an exemption from the EA requirement under categorical exclusion is acceptable.

III. Administrative

- **A. Reviewer's Signature**

  Signed in DFS by Rao V. Kambhampati, Ph.D., Senior Regulatory Review Scientist (Chemist).

- **B. Endorsement Block**

  Signed in DFS by Norman Schmuff, Ph.D., Branch Chief, Branch IV, DPA II, ONDQA.

- **C. CC Blockcc:**

  Org. NDA 21-976
  HFD-800/Branch Chief/NSchmuff
  HFD-530/PM/EThompson
  HFD-800/Chem Reviewer/RKambhampati
  HFD-800/PAL/SMiller
  HFD-800/PM/KStiller

39 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 1

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

/s/

Rao Kambhampati
6/23/2006 03:44:17 PM
CHEMIST
Recommended for approval.
Please sign off and file.

Norman Schmuff
6/23/2006 04:04:40 PM
CHEMIST