

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202895Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 202-895**

**Prezista<sup>™</sup>  
(darunavir)  
Oral Suspension  
100 mg per mL**

**Tibotec, Inc.**

**Mark R. Seggel  
ONDQA  
Division of New Drug Quality Assessment II  
Branch V**

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2. REVIEW #: 2
3. REVIEW DATE: 28-SEP-2011
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u> (eCTD)		<u>Document Date</u>
Original submission	(0000)	29-MAR-2011
Amendment (mfg. facilities)	(0003)	26-APR-2011
Amendment (response to info. request)	(0019)	29-JUL-2011
Amendment (response to info. request)	(0024)	18-AUG-2011
Amendment (response to info. request)	(0025)	19-AUG-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u> (eCTD)		<u>Document Date</u>
Amendment (labeling)	(0030)	08-SEP-2011
Amendment (CMC)	(0031)	09-SEP-2011
Amendment (alternative dosing pipette)	(0032)	09-SEP-2011
Amendment (labeling)	(0033)	09-SEP-2011
Amendment (labeling)	(0034)	12-SEP-2011
Amendment (alternative dosing pipette)	(0035)	14-SEP-2011
Amendment (labeling)	(0036)	21-SEP-2011
Amendment (syringe graphics)	(0037)	22-SEP-2011
Amendment (labeling)	(0040)	28-SEP-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Tibotec, Inc.
Address:	920 U.S. Highway 202, P.O. Box 300 Raritan, NJ 08869-0602
Representative(s):	Charles Zezza, PhD Director, Global Regulatory Affairs
Telephone:	908-707-3451

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Prezista™
- b) Non-Proprietary Name (USAN): Darunavir
- c) Code Name/#: TMC114 (TMC114 ethanolate); R319064; JNJ-25875382; 54179
- d) CAS Registry Number: ethanolate: 635728-49-3; (b) (4): 206361-99-1

## Chemistry Review Data Sheet

e) Chem. Type/Submission Priority:

- i. Chem. Type: 3
- ii. Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)

10. PHARMACOL. CATEGORY: Antiretroviral/Systemic/HIV/Protease inhibitor (7030220)

11. DOSAGE FORM: Suspension

12. STRENGTH/POTENCY: 100 mg per mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

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

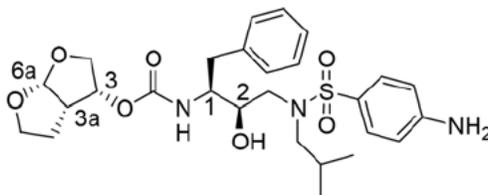
 SPOTS product – Form Completed Not a SPOTS product16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT

Chemical Names:

1. [(1*S*,2*R*)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl ester
2. Carbamic acid, [(1*S*,2*R*)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl ester

USAN/INN: Darunavir

Structural Formula:



Molecular Formula and Molecular Weight:

Darunavir	$C_{27}H_{37}N_3O_7S$	547.66	
Darunavir ethanolate	$C_{27}H_{37}N_3O_7S \cdot C_2H_6O$	593.73	(b) (4) by weight)

Note: The labeled strength, 100 mg/mL, is based on the weight of darunavir.

## Chemistry Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS**
**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
18825	II	Janssen Pharmaceutica NV (J&J PR&D)	Darunavir API	1	Adequate	31-AUG-2011	covering (b) (4) and particle size control (b) (4)

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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

APPLICATION NUMBER	SUBJECT
NDA 21-976	Darunavir Tablets; Approved 23-JUN-2006

**18. STATUS**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Recommendation: Acceptable	20-MAY-2011	D. Smith
Pharm/Tox	N/A		
ONDQA Biopharmaceutics	Interim dissolution test acceptance criterion acceptable	01-SEP-2011	M. Seggel
LNC	N/A		
Methods Validation	N/A		
DMEPA	Labeling revisions recommended; Use of standard oral syringe and bottle adaptor/plug recommended.	31-AUG-2011	L. Holmes
DRISK	Labeling revisions recommended Labeling revisions recommended	06-SEP-2011 28-SEP-2011	S. Morin “
EA	Categorical exclusion acceptable	06-SEP-2011	M. Seggel
Quality Microbiology	Recommend approval	10-AUG-2011	J. Metcalf

**19. GOAL DATES      PDUFA Goal:    30-SEP-2011**

# The Chemistry Review for NDA 202-895

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient information to assure identity, strength, quality, purity, potency and bioavailability of the drug product. The labels have adequate information as required. The issues regarding the dosing device and labeling identified in Chemistry Review #1 have been resolved. The Office of Compliance has issued an overall recommendation of 'Acceptable' based on the satisfactory cGMP status of the manufacturing facilities. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

Tibotec and the ONDQA Biopharmaceutics review team have agreed to the establishment of an Interim dissolution test acceptance criterion. A Q of  $\frac{(b)}{(4)}\%$  at 45 minutes will be in place while Tibotec continues to collect dissolution profiles at release and on stability for one (1) year following approval. Per a Post-Marketing Commitment, Tibotec will report the results and propose a final regulatory specification for review. See this reviewer's Biopharmaceutics review for background information.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

PREZISTA (darunavir) Oral Suspension, 100 mg/mL is a  $\frac{(b)}{(4)}$ , white to off-white opaque, strawberry-cream flavored liquid containing the equivalent of 100 mg darunavir per mL. The suspension is supplied in amber-colored multiple-dose bottles containing 200 mL of the liquid. Note that while the product is manufactured from darunavir ethanolate, in aqueous systems such as the suspension, the ethanolate undergoes conversion to the iso-structural hydrate. This interconversion does not affect bioavailability.

Darunavir is currently available in tablet form (NDA 21-976). The first approved tablet strength was 300 mg (AP 23-JUN-2006). Subsequently, a 600 mg tablet was approved (25-FEB-2008); this is the current RLD. A 400 mg tablet was approved on 21-OCT-2008. This was followed by approval of 75 mg and 150 mg tablets on 18-DEC-2008. The 300 mg tablet is no longer marketed in the U.S. Darunavir oral suspension was developed in order to address the needs of pediatric patients unable to swallow Prezista

## Executive Summary Section

(darunavir) Tablets and to provide a product suitable for young children (age 3-6 years).

Initially, development focused on a (b) (4) mg/mL formulation, but a 100 mg/mL product was preferable, allowing a smaller volume to provide the required dose.

The overall drug product quality control strategy encompasses everything from drug substance characteristics, excipient selection and controls, product composition, manufacturing process controls, release testing, container-closure system characteristics, and stability testing.

Inactive ingredients in darunavir oral suspension consist of hydroxypropyl cellulose (b) (4), microcrystalline cellulose and (b) (4) (b) (4); selected to give a product with (b) (4), (b) (4), (b) (4), (b) (4), (b) (4), citric acid monohydrate, sucralose, masking flavor, strawberry cream flavor (darunavir has an (b) (4) (b) (4) hydrochloric acid and purified water. All are commonly used in oral formulations and are of suitable quality for use in this product. All except the flavors are controlled in accordance with compendial monographs.

The manufacturing process is relatively straightforward; essentially a (b) (4)

The regulatory specification for Prezista Oral Suspension includes tests for identity, assay, chromatographic impurities, pH (critical for optimal (b) (4) effectiveness), deliverable volume, and dissolution rate (an interim acceptance criterion for dissolution has been established; see this reviewer's ONDQA Biopharmaceutics review of the dissolution test method and data). The specification also includes an assay of methylparaben, (b) (4).

Darunavir oral suspension is packaged in an amber glass bottle with (b) (4), (b) (4) cap. This container-closure system provides adequate protection of the product (including light protection, as some components of the flavors may be light sensitive). The (b) (4) closure provides an appropriate level of safety. A 6-mL (b) (4) oral syringe and bottle adapter are included in the carton with each bottle.

The stability of three registration batches of darunavir oral suspension at 25°C/40% RH has been followed through 12 months. No significant changes in product quality attributes are noted, although there is a slight decrease in percent dissolved at 30 minutes (see ONDQA Biopharmaceutics review). These studies are ongoing to confirm the proposed 24-month expiration dating period of the drug product.

## Executive Summary Section

Storage under refrigeration and freezing conditions were conducted. Refrigeration can result in precipitation of methylparaben, and thus should be avoided. Temperature cycling studies were also conducted. No adverse effects were noted. Initial results from an ongoing simulated in-use study indicate that repeated opening of the bottle and removal of a dose does not adversely affect the quality of the product.

(b) (4) effectiveness testing demonstrated that the product meets the (b) (4) criteria for oral products made with an aqueous base. Adequate product quality microbiology controls have been established, and include tests for

(b) (4)  
(see Product Quality Microbiology review for details.)

Darunavir API is (b) (4). The chemistry, manufacture and control (CMC) of darunavir ethanolate drug substance used in the manufacture of both darunavir tablets and darunavir oral suspension is documented in Janssen Pharmaceutica's DMF 18825. Darunavir is only very slightly (b) (4). Other than a (b) (4) the CMC is the same. Drug substance particle size, although not particularly critical to bioavailability, can (b) (4). Hence, the drug substance is (b) (4) in the manufacture of the suspension.

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

Prezista is indicated for the treatment of HIV-1 infections in adult patients. It is also indicated for the treatment of HIV-1 infection in pediatric patients 3 years of age and older. Prezista must be co-administered with ritonavir and with other antiretroviral agents. Darunavir is taken twice daily with food. In patients weighing 10 to 15 kg (22 to 33 pounds), the weight-based dose is (b) (4) mg/kg (equivalent to (b) (4) mL of the oral suspension]). Dosing of patients greater than 15 kg is also described. The maximum dose of 800 mg (8 mL; for adults unable to swallow the tablets) should be taken as two 4 mL administrations with the included oral dosing syringe.

Prezista Oral Suspension is supplied in amber glass bottles with (b) (4) caps. A 6-mL (b) (4) oral syringe and bottle adapter will be supplied with the bottle. (Note: The originally proposed (b) (4) will not be used with product in the U.S.) The patient or caregiver will press fit the adapter into the bottle neck. The tip of the syringe is inserted into the adapter and the bottle inverted. The required dose is withdrawn into the syringe. The syringe is removed from the adapter and the dose administered.

Prezista Oral Suspension is labeled for storage at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F). The label also indicates that the product should not be refrigerated or frozen. Exposure to excessive heat is to be avoided. The suspension is to be stored in the original container, and should be shaken well before each usage.

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

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The applicant also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

The proposed dissolution test acceptance criterion,  $Q = \frac{(b)}{(4)}\%$  at 30 minutes was considered unacceptable. While the available release and stability data suggest that  $Q = \frac{(b)}{(4)}\%$  at 30 minutes is appropriate (although some Stage 2 testing may be necessary), Tibotec concludes that an unacceptably high overall failure rate will occur at the proposed 24-month expiry (see Biopharmaceutics review). An Interim acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at 45 minutes has been established. This will ensure that a mean of at least  $\frac{(b)}{(4)}\%$  of the drug product is dissolved. A Post-Marketing Commitment (PMC) addresses the requirements for collecting data for one year and proposal of a final regulatory acceptance criterion.

Prezista Oral Suspension is supplied in amber glass bottles with  $\frac{(b)}{(4)}$  caps. A dosing device is supplied with each bottle of oral suspension. The originally proposed  $\frac{(b)}{(4)}$ , reviewed in Chemistry Review #1 will not be used with product in the U.S. DMEPA determined that the design of that  $\frac{(b)}{(4)}$  was inconsistent with what patients in the U.S. are familiar with and was likely to lead to confusion and dosing errors. An alternative oral syringe and adapter was subsequently proposed and is documented in the present review. A 6-mL  $\frac{(b)}{(4)}$  oral syringe and bottle adapter will be supplied with the bottle. The materials of construction comply with  $\frac{(b)}{(4)}$ , which  $\frac{(b)}{(4)}$ . Dosing accuracy of the oral syringe is within  $\pm 5\%$  across the dosage range of 2.6 mL to 6 mL. Reference is also made to Type III DMF  $\frac{(b)}{(4)}$  covering the oral syringe and bottle adapter. DMEPA finds the proposed oral syringe acceptable.

Labeling for this product consists of the bottle label, carton, package insert, patient information, directions for use (lacking at the time Chemistry Review # was completed) and syringe graphics. All labels have the required Description, How Supplied and Storage information. The trademark, Prezista, was previously found acceptable for Tibotec's formulations of darunavir (i.e., Prezista Tablets). DMEPA and DRISK have provided recommendations for revisions to all components of the labeling. For example, it was recommended that the strength be expressed as "100 mg per mL" rather than "100 mg/mL". In addition, DMEPA recommended that the storage and handling statements (e.g., 'Do not refrigerate or freeze') be made more prominent. See DMEPA

## Executive Summary Section

review dated 31-AUG-2011 and DRISK reviews dated 06-SEP-2011 and 28-Sep-2011. From the CMC perspective, all labeling recommendations made to date are acceptable.

Finally, all manufacturing, packaging and testing facilities have acceptable site recommendations. An overall recommendation of Acceptable was issued by the Office of Compliance on 20-MAY-2011 (see Chemistry Review #1).

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

*{see electronic signature page}*

**B. Endorsement Block**

*{see electronic signature page}*

**C. CC Block**

*{see darrts}*

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/s/  
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MARK R SEGCEL  
09/29/2011

RAPTI D MADURAWA  
09/29/2011

**NDA 202-895**

**Prezista<sup>™</sup>**  
**(darunavir)**  
**Oral Suspension**  
**100 mg/mL**

**Tibotec, Inc.**

**Mark R. Seggel**  
**ONDQA**  
**Division of New Drug Quality Assessment II**  
**Branch V**

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# Chemistry Review Data Sheet

1. NDA 202-895
2. REVIEW #: 1
3. REVIEW DATE: 06-SEP-2011
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

Previous Documents  
Not Applicable

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)

Original submission (0000)  
 Amendment (mfg. facilities) (0003)  
 Amendment (response to info. request) (0019)  
 Amendment (response to info. request) (0024)  
 Amendment (response to info. request) (0025)

Document Date

29-MAR-2011  
 26-APR-2011  
 29-JUL-2011  
 18-AUG-2011  
 19-AUG-2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Tibotec, Inc.
Address:	920 U.S. Highway 202, P.O. Box 300 Raritan, NJ 08869-0602
Representative(s):	Charles Zezza, PhD Director, Global Regulatory Affairs
Telephone:	908-707-3451

8. DRUG PRODUCT NAME/CODE/TYPE:
  - a) Proprietary Name: Prezista™
  - b) Non-Proprietary Name (USAN): Darunavir
  - c) Code Name/#: TMC114 (TMC114 ethanolate); R319064; JNJ-25875382; 54179
  - d) CAS Registry Number: xxx
  - e) Chem. Type/Submission Priority:
    - i. Chem. Type: 3
    - ii. Submission Priority: P
9. LEGAL BASIS FOR SUBMISSION: 505(b)

## Chemistry Review Data Sheet

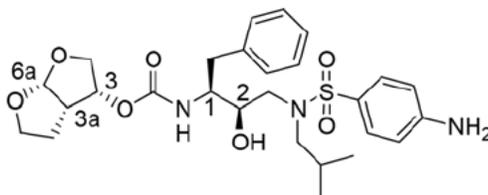
10. PHARMACOL. CATEGORY: Antiretroviral/Systemic/HIV/Protease inhibitor (7030220)
11. DOSAGE FORM: Suspension
12. STRENGTH/POTENCY: 100 mg/mL
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)  
 SPOTS product – Form Completed  
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
 MOLECULAR WEIGHT

## Chemical Names:

- [(1*S*,2*R*)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl ester
- Carbamic acid, [(1*S*,2*R*)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl ester

USAN/INN: Darunavir

## Structural Formula:



## Molecular Formula and Molecular Weight:

Darunavir	$C_{27}H_{37}N_3O_7S$	547.66
Darunavir ethanolate	$C_{27}H_{37}N_3O_7S \cdot C_2H_6O$	593.73 ( (b) (4) by weight)

Note: The labeled strength, 100 mg/mL, is based on the weight of darunavir.

## 17. RELATED/SUPPORTING DOCUMENTS

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
18825	II	Janssen	Darunavir API	1	Adequate	31-AUG-2011	covering (b) (4)

## Chemistry Review Data Sheet

	Pharmaceutica NV (J&J PR&D)					and particle size control
(b) (4)						

<sup>1</sup> 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")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

APPLICATION NUMBER	SUBJECT
NDA 21-976	Darunavir Tablets; Approved 23-JUN-2006

### 18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Overall Recommendation: Acceptable	20-MAY-2011	D. Smith
Pharm/Tox	N/A		
ONDQA Biopharmaceutics	Interim dissolution test acceptance criterion acceptable	01-SEP-2011	M. Seggel
LNC	N/A		
Methods Validation	N/A		
DMEPA	Labeling revisions recommended; Use of standard oral syringe and bottle adapter/plug recommended.	31-AUG-2011	L. Holmes
EA	Categorical exclusion acceptable	06-SEP-2011	M. Seggel
Quality Microbiology	Recommend approval	10-AUG-2011	J. Metcalf

### 19. GOAL DATES

**GRMP Goal:** 06-SEP-2011

**PDUFA Goal:** 30-SEP-2011

# The Chemistry Review for NDA 202-895

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA, as amended, has provided sufficient information to assure the identity, strength, quality, purity, potency and bioavailability of the drug product. The Office of Compliance has issued an overall recommendation of 'Acceptable' based on the satisfactory cGMP status of the manufacturing facilities. From the CMC perspective, a recommendation for approval of this NDA can be made upon satisfactory resolution of the following pending issues:

- Dosing syringe - DMEPA strongly recommends that the proposed (b) (4) be replaced with a standard oral dosing syringe. Tibotec will be providing a proposal for a new dosing syringe with updated Directions for Use and documentation of suitability.
- Labeling - Although the 'CMC content' of the labeling is factually correct, DMEPA has recommended certain changes regarding the expression of strength and increasing prominence of handling statements. Labeling is pending team review.

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

Tibotec and the Biopharmaceutics review team have agreed to the establishment of an Interim dissolution test acceptance criterion. A Q of (b) (4) % at 45 minutes will be in place while Tibotec continues to collect dissolution profiles at release and on stability. After one (1) year, Tibotec will report the results and propose a final regulatory specification for review. See this reviewer's Biopharmaceutics review for background information. Exact wording of the agreement is being worked out with Tibotec; they will then submit documentation of the final agreement.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

PREZISTA (darunavir) Oral Suspension, 100 mg/mL is a (b) (4), white to off-white opaque, strawberry-cream flavored liquid containing the equivalent of 100 mg darunavir per mL. The suspension is supplied in amber-colored multiple-dose bottles containing 200 mL of the liquid. Note that while the product is manufactured from darunavir ethanolate, in aqueous systems such as the suspension, the ethanolate undergoes conversion to the iso-structural hydrate. This interconversion does not affect bioavailability.

Darunavir is currently available in tablet form (NDA 21-976). The first approved tablet strength was 300 mg (AP 23-JUN-2006). Subsequently, a 600 mg tablet was approved (25-FEB-2008); this is the current RLD. A 400 mg tablet was approved on 21-OCT-2008. This was followed by approval of 75 mg and 150 mg tablets on 18-DEC-2008. The 300 mg tablet is no longer marketed in the U.S. Darunavir oral suspension was developed in order to address the needs of pediatric patients unable to swallow Prezista (darunavir) Tablets and to provide a product suitable for young children (age 3-6 years).

Initially, development focused on a (b) (4) mg/mL formulation, but a 100 mg/mL product was preferable, allowing a smaller volume to provide the required dose.

The overall drug product quality control strategy encompasses everything from drug substance characteristics, excipient selection and controls, product composition, manufacturing process controls, release testing, container-closure system characteristics, and stability testing.

Inactive ingredients in darunavir oral suspension consist of hydroxypropyl cellulose (b) (4), microcrystalline cellulose and carmellose sodium (b) (4); (b) (4); (b) (4) citric acid monohydrate, sucralose, masking flavor, strawberry cream flavor (darunavir (b) (4)), (b) (4) hydrochloric acid and purified water. All are commonly used in oral formulations and are of suitable quality for use in this product. All except the flavors are controlled in accordance with compendial monographs.

The manufacturing process is relatively straightforward; essentially (b) (4)

The regulatory specification for Prezista Oral Suspension includes tests for identity, assay, chromatographic impurities, pH (critical for optimal (b) (4) effectiveness), deliverable volume, and dissolution rate (an interim acceptance criterion for dissolution has been established; see this reviewer's ONDQA Biopharmaceutics review of the dissolution test method and data). The specification also includes an assay of methylparaben, (b) (4)

Darunavir oral suspension is packaged in an amber glass bottle with (b) (4), (b) (4) evident cap. This container-closure system provides adequate protection of the product (including light protection, as some components of the flavors may be light sensitive). The (b) (4) closure provides an appropriate level of safety.

## Executive Summary Section

The stability of three registration batches of darunavir oral suspension at 25°C/40% RH has been followed through 12 months. No significant changes in product quality attributes are noted, although there is a slight decrease in percent dissolved at 30 minutes (see ONDQA Biopharmaceutics review). These studies are ongoing to confirm the proposed 24-month expiration dating period of the drug product.

Storage under refrigeration and freezing conditions were conducted. Refrigeration can result in precipitation of methylparaben, and thus should be avoided. Temperature cycling studies were also conducted. No adverse effects were noted. Initial results from an ongoing simulated in-use study indicate that repeated opening of the bottle and removal of a dose does not adversely affect the quality of the product.

(b) (4) effectiveness testing demonstrated that the product meets the (b) (4) criteria for oral products made with an aqueous base. Adequate product quality microbiology controls have been established, and include tests for microbiological purity (b) (4) and other objectionable organisms). The currently available stability data, including in-use testing, indicate that the microbiological purity can be maintained at an acceptable level during storage and use (ca. 6 weeks) (see Product Quality Microbiology review for details.)

Darunavir API is (b) (4). The chemistry, manufacture and control (CMC) of darunavir ethanolate drug substance used in the manufacture of both darunavir tablets and darunavir oral suspension is documented in Janssen Pharmaceutica's DMF 18825. Darunavir is only very (b) (4). Other than a (b) (4) the API specification, the CMC is the same. Drug substance particle size, although not particularly critical to bioavailability, can influence (b) (4). Hence, the drug substance is (b) (4).

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

Prezista is indicated for the treatment of HIV-1 infections in adult patients. It is also indicated for the treatment of HIV-1 infection in pediatric patients 3 years of age and older. Prezista must be co-administered with ritonavir and with other antiretroviral agents. Darunavir is taken twice daily with food. In patients weighing 10 to 15 kg (22 to 33 pounds), the weight-based dose is (b) (4) mg/kg (equivalent to 260 - 360 mg [2.6 - 3.6 mL of the oral suspension]).

Prezista Oral Suspension is supplied in amber glass bottles with (b) (4) caps. Tibotec intended to include a six milliliter plastic dosing (b) (4) with the product. However, based on concerns with this atypical, at least in the U.S., syringe, Tibotec

was asked to propose an alternative means for accurately measuring and administering the requisite volumes of oral suspension.

Prezista Oral Suspension is labeled for storage at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F). The label also indicates that the product should not be refrigerated or frozen. Exposure to excessive heat is to be avoided. The suspension is to be stored in the original container, and should be shaken well before each usage.

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

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The applicant also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

The proposed dissolution test acceptance criterion,  $Q = \frac{(b)}{(4)}\%$  at 30 minutes was considered unacceptable. While the available release and stability data suggest that  $Q = \frac{(b)}{(4)}\%$  at 30 minutes is appropriate (although some Stage 2 testing may be necessary), Tibotec concludes that an unacceptably high overall failure rate will occur at the proposed 24-month expiry (see Biopharmaceutics review). An Interim acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at 45 minutes has been established. This will ensure that a mean of at least  $\frac{(b)}{(4)}\%$  of the drug product is dissolved. A post Marketing Commitment will address the requirements for collecting data for one year and proposal of a final regulatory acceptance criterion.

DMEPA has requested that proposed dosing  $\frac{(b)}{(4)}$  (6 mL capacity;  $\frac{(b)}{(4)}$  graduations) not be used to administer the drug product because of the potential dosing errors resulting from confusion in how to use it. Unlike a standard oral syringe, the graduations on the proposed syringe are  $\frac{(b)}{(4)}$ . It should be noted that the proposed dosing  $\frac{(b)}{(4)}$  has a nominal accuracy of  $\frac{(b)}{(4)}\%$ . Accuracy across the range 2.6 mL to 6.0 mL was measured, using suspension,

DMEPA recommends that a standard oral syringe and plug (bottle adapter) be provided with the oral suspension. The applicant is currently trying to locate and qualify a suitable replacement. Documentation to support the syringe should include identification of the  $\frac{(b)}{(4)}$  or a statement of compliance of the materials of construction of the syringe and adapter with 21 CFR 177, for example. Data demonstrating the dosing accuracy of the syringe would facilitate an assessment of the suitability of the syringe. Evidence that the syringe and adapter are already used in commerce could be helpful. Ideally, the syringe will be documented in a Type III Drug Master File. Whatever dosing device is finally accepted, the labeling will need to include adequate directions for use.

## Executive Summary Section

Because the currently proposed [REDACTED] <sup>(b) (4)</sup> also serves as part of the bottle seal, if this configuration is changed, an alternative seal will need to be introduced and seal integrity demonstrated.

All labels have the required Description and How Supplied information. However, directions for use and cleaning of the currently proposed dosing [REDACTED] <sup>(b) (4)</sup> were not provided. The trademark, Prezista, was previously found acceptable for Tibotec's formulations of darunavir (i.e., Prezista Tablets). DMEPA has provided recommendations for revisions to the Container and Carton labeling. Specifically, they recommend that the strength be expressed as "100 mg per mL" rather than "100 mg/mL". In addition, DMEPA recommends that the storage and handling statements (e.g., 'Do not refrigerate or freeze') be made more prominent. See DMEPA review dated 32-AUG-2011. From the CMC perspective, the recommendations are acceptable.

Finally, all drug substance and drug product manufacturing, packaging and testing facilities have acceptable site recommendations. An overall recommendation of Acceptable was issued by the Office of Compliance on 20-MAY-2011 (see attached EES Report).

### III. Administrative

#### A. Reviewer's Signature

*{see electronic signature page}*

#### B. Endorsement Block

*{see electronic signature page}*

#### C. CC Block

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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.**  
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/s/  
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MARK R SEGCEL  
09/06/2011

RAPTI D MADURAWA  
09/06/2011

# CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

**Filing Checklist**

		<b>Established/Proper Name:</b>
<b>NDA Number: 202-895</b>	<b>Supplement Number and Type:</b>	<b>Prezista (darunavir) Oral Suspension</b>
	N/A	<b>100 mg/mL</b>
<b>Applicant: Tibotec, Inc.</b>	<b>Letter Date: March 30, 2011</b>	<b>Stamp Date: March 30, 2011</b>

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR NDA/BLA or Supplement**

6.	<p>For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b></p>			N/A
7.	<p>Are drug substances manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	✓		Attachment to FDA Form 356h dated March 29, 2011.

## CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	✓		Attachment to FDA Form 356h dated March 29, 2011.
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	✓		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	✓		Provided in the FDA Form 356h dated March 29, 2011.

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR NDA/BLA or Supplement**

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		Request for categorical exclusion.

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?			Reference to DMF Type II 18825 (LoA provided in section dated March 9, 2011).
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See above
14.	Does the section contain information regarding the characterization of the DS?			See above
15.	Does the section contain controls for the DS?			See above
16.	Has stability data and analysis been provided for the drug substance?			See above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			See above
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			See above

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR NDA/BLA or Supplement**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		Executed production records for one batch (b) (4) (b) (4) L) have been provided in section 3.2.R.1.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?			
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		(b) (4) -mL amber glass bottle with (b) (4) and (b) (4) closure and insert
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		Stability data provided (12 month primary and 6-week in-use stability data).
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			<i>Description of the formulation and manufacturing process optimization in P.2 (discussion of COAs, PARs, etc.).</i>
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			Not obvious.

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	✓		Section 3.2.P.5.3

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR NDA/BLA or Supplement**

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			N/A (non-sterile product)

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		See table below.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE
18825	II	Johnson & Johnson	Darunavir	March 9, 2011
(b) (4)				

<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		Bottle and carton labels provided in section 1.14.1.1.

<b>J. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			N/A

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR NDA/BLA or Supplement**

36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		✓	<i>Not yet identified.</i>
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*{See appended electronic signature page}*

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Dorota Matecka, Ph.D.  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

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Rapti Madurawe, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment

Date

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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.**  
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/s/  
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DOROTA M MATECKA  
05/02/2011

RAPTI D MADURawe  
05/02/2011