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RESEARCH**

*APPLICATION NUMBER:*

**202895Orig1s000**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

09 August 2011

**NDA:** 202-895/N-000

**Drug Product Name**

**Proprietary:** Prezista®.

**Non-proprietary:** Darunavir.

**Review Number:** 1.

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
29 MAR 2011	30 MAR 2011	20 APR 2011	21 APR 2011
15 JUN 2011	15 JUN 2011	N/A	N/A

**Applicant/Sponsor**

**Name:** Tibotec, Inc.

**Address:** 1125 Trenton-Harbourton Rd.  
Tutusville, NJ 08560

**Representative:** Charles Zezza, Ph.D.

**Telephone:** 908-707-3451

**Name of Reviewer:** John W. Metcalfe, Ph.D.

**Conclusion:** Recommend approval.

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## Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** 505(b)(1) NDA.
2. **SUBMISSION PROVIDES FOR:** A pediatric formulation based on an approved tablet formulation (reference is made to NDA 21-976).
3. **MANUFACTURING SITE:**  
Janssen Pharmaceutica NV  
Turnhoutseweg 30  
Beerse B-2340  
Belgium
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**  
➤ Suspension.  
➤ Oral.  
➤ 100 mg/mL.
5. **METHOD(S) OF STERILIZATION:** The drug product is not sterile.
6. **PHARMACOLOGICAL CATEGORY:** Antiviral.
- B. **SUPPORTING/RELATED DOCUMENTS:** None.
- C. **REMARKS:**  
The subject NDA is submitted electronically in the CTD format.

A Microbiology Information request was forwarded to the applicant by the ONDQA Project Manager on 25 May 2011. Following is the reviewer comments and information requests:

Reference is made to Table 1 (*Specifications for the drug Product (F052)*) of Module 3.2.P.5.1 which states the following regarding the product specification and microbiological testing, “monitoring frequency based on microbiological risk assessment”. Further reference is made to Section 1.8 of Module 3.2.P.5.6 (*Justification of Specifications*) which states, “the drug product is tested and validated for microbiological purity according to the requirements of current USP<61> and <62>”.

This microbiology reviewer notes that the microbiological risk assessment referenced in the Product Specification was not provided in the application. In addition, the application lacks verification studies demonstrating the suitability of use of the stated microbial limits tests with the subject drug product. Finally, for aqueous non-sterile dosage forms,

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*Burkholderia cepacia* is considered to be an objectionable microorganism, in addition to the objectionable organisms listed in USP<1111>.

- Clarify whether microbial limits testing will be performed as part of the release testing of every product batch.
- Provide the microbial test methods and data sets which verify the suitability of use of these tests (both microbial enumeration and specified microbes) with the subject drug product.
- It is understood that the product specification references USP<1111> regarding microbial limits acceptance criteria. Modify the product specification to specify the numerical limits and identities of each of the organisms that will be tested for regarding microbial limits acceptance criteria.
- Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

The applicant amended the application with responses to this Information Request on 15 June 2011. Applicant responses are summarized and reviewed in appropriate sections of this review.

A second Microbiology Information Request was forwarded to the applicant on 27 June 2011 by the OND Project Manager. Following is the Information Request:

Reference is made to the FDA Information Request dated 25 May 2011 regarding microbial limits testing for Prezista<sup>®</sup>. Further reference is made to Tibotec's responses to this request submitted on 15 June 2011.

Tibotec's responses to FDA Request # 1, and 2 are acceptable. Regarding FDA Request #3, add "absence of *Burkholderia cepacia*" to the list of Specified Microorganisms identified in the product specification. With regard to FDA Request #4, Tibotec has not demonstrated the ability to recover the objectionable organism *Burkholderia cepacia* from the subject drug product, nor has Tibotec provided a validated test for the detection of this organism, as requested. Provide a test method for detecting *B. cepacia* similar to the one you have provided for the specified organism, *Escherichia coli*. The original FDA Request #4 is copied below for Tibotec's convenience.

Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

The applicant amended the application with responses to Microbiology Information Request #2 on 29 July 2011. Applicant responses are summarized and reviewed in appropriate sections of this review.

**File Name:** N202895N000R1.doc

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**Executive Summary**

**I. Recommendations**

- A. **Recommendation on Approvability** – NDA 202-895/N-000 is recommended for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

**II. Summary of Microbiology Assessments**

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** -  (b) (4)
- B. **Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

**III. Administrative**

- A. **Reviewer's Signature** \_\_\_\_\_  
John W. Metcalfe, Ph.D.
- B. **Endorsement Block** \_\_\_\_\_  
Bryan S. Riley, Ph.D.
- C. **CC Block**  
N/A

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/s/  
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JOHN W METCALFE  
08/10/2011

BRYAN S RILEY  
08/10/2011  
I concur.

**DIVISION OF ANTIVIRAL PRODUCTS  
OFFICE OF NEW DRUGS  
VIROLOGY REVIEW**

**NDA: 202,895 SN: 000 DATE REVIEW COMPLETE: 4/29/11**

**Virology Reviewer: Lisa K. Naeger, Ph.D.**

**NDA#:** 202,895

**Serial #:** 000

**Reviewer's Name:** Lisa K. Naeger, Ph.D.

**Sponsor's Name and Address:** Tibotec-Virco, USA  
2505 Meridian Parkway  
Suite 350  
Durham, NC 27713

**Important Dates:**

**Correspondence Date:** March 28, 2011  
**CDER Receipt Date:** March 30, 2011  
**Assigned Date:** March 30, 2011  
**Review Complete Date:** April 29, 2011  
**PDUFA Date:** September 30, 2011

**Amendments:** none

**Related/Supporting Documents:** IND-62477, NDA-21976 SN000, NDA-21976 SN006, SN007 and SN009

**Product Name(s)**

**Proprietary:** PREZISTA/rtv

**Non-Proprietary/USAN:** Darunavir/rtv; darunavir

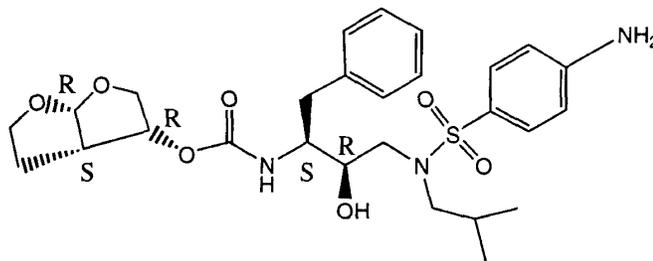
**Code Name/Number:** TMC114

**Empirical formula:** C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>S .C<sub>2</sub>H<sub>5</sub>OH

**Chemical Name:** {3-[(4-amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-carbamic acid hexahydro-furo-[2,3-b]furan-3-yl ester.ethanolate

**Molecular mass:** Relative molecular mass: 547.656 (active moiety) + 46.068 (ethanol, EtOH) = 593.724 (TMC 114-ethanolate)

**Structural Formula:**



**Darunavir**

**Drug category:** antiviral for HIV infection

**Dosage Form(s):** Oral; co-administration with ritonavir

**Route(s) of Administration:** Oral

**DIVISION OF ANTIVIRAL PRODUCTS  
OFFICE OF NEW DRUGS  
VIROLOGY REVIEW**

**NDA: 202,895 SN: 000 DATE REVIEW COMPLETE: 4/29/11**

**Virology Reviewer: Lisa K. Naeger, Ph.D.**

**Dispensed: Rx   X   OTC**

**Abbreviations:** ABC, abacavir; APV, amprenavir; ATV, atazanavir; AZT, zidovudine; Control, comparator PI arm; ddl, didanosine; d4T, stavudine; DRV, darunavir; EFV, efavirenz; ETR, etravirine; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus-1; IC, inhibitory concentration; IDV, indinavir; LAM, lamivudine; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBT, optimized background therapy; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PI, protease inhibitor; /rtv, ritonavir-boosted; RT, reverse transcriptase; SQV, saquinavir; ENF, enfuvirtide; TDF, tenofovir; TPV, tipranavir

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***EXECUTIVE SUMMARY***

Darunavir (DRV) is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles. It was approved June 23, 2006 for combination antiretroviral treatment of HIV-1 infected treatment-experienced adult subjects. The supplemental NDA with 96-week data of DRV/r treatment from studies of treatment-experienced subjects and 48-week data of DRV/r treatment from studies of treatment-naïve subjects was approved October 21, 2008. DRV is currently approved for treatment-experienced HIV-1 infected children >6 years old. This supplemental pediatric NDA seeks approval for treatment-experienced children 3 to <6 years old.

This submission contains Week 24 efficacy, safety and PK data from the open-label Phase II trial TMC114-C228 (ARIEL) to support the selected pediatric doses of darunavir with low-dose ritonavir (DRV/r), by body weight, in combination with other antiretroviral (ARV) products, in treatment-experienced HIV-1-infected children from 3 to <6 years of age and weighing between 10 and <20 kg. Approximately 24 children, on a stable ARV treatment for ≥12 weeks but who needed to change their ARV regimen because it was currently failing (plasma viral load >1,000 copies/mL), and who had <3 DRV resistance-associated substitutions, were planned to be included in the trial with ≥10 and maximally 14 children for each of the 2 following weight bands: 10 to <15 kg and 15 to <20 kg. Subjects were initially to be given a dose of DRV/r 20/3 mg/kg twice daily, together with an OBR consisting of ≥2 active ARVs with available pediatric dose recommendations.

At baseline, 2 subject isolates harbored DRV substitutions (PID 228-0009 had L33F and L76V, and PID 228-0015 had L76V). Both subjects responded virologically (HIV-1 RNA <50 copies/mL) at Week 24.

Post-baseline resistance testing was performed on samples with plasma viral load ≥50 copies/mL. There were 11 (41%) never-suppressed subjects, when using the virologic response parameter plasma viral load <50 copies/mL (TLOVR non-VF censored) over time (1 subject discontinued due to an AE). When using the virologic response parameter confirmed plasma viral load <400 copies/mL (TLOVR non-VF censored), 9 out of these 11 never-suppressed subjects were considered responders, of whom 7 had



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/s/  
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LISA K NAEGER  
05/24/2011

JULIAN J O'REAR  
05/25/2011

## MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

**NDA Number:** 202-895

**Applicant:** Tibotec

**Stamp Date:** March 29, 2011

**Drug Name:** Prezista  
(darunavir)

**NDA Type:** Pediatric

On **initial** overview of the NDA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant <u>submitted</u> cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			n/a
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			n/a
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?			n/a
7	Has the applicant <u>submitted</u> the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?		X	n/a
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?			n/a
9	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
10	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?			n/a
11	Have all the study reports, published articles, and other			n/a

File name: 5\_Microbiology Filing Checklist for a NDA or Supplement 010908

## MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	references been included and cross-referenced in the annotated draft labeling or summary section of the submission?			
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

**IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE?** Yes

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

\_\_\_\_\_  
 Lisa K. Naeger 4/26/11  
 Reviewing Microbiologist Date

\_\_\_\_\_  
 Microbiology Team Leader Date

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/s/  
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LISA K NAEGER  
04/26/2011

JULIAN J O'REAR  
04/26/2011