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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

Submit	Received	Review Request	Assigned to Reviewer
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.

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,

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®. Further reference is made to Tibotec's responses to this request submitted on 15 June 2011.

Tibotek'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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