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APPLICATION NUMBER:

202895Orig1s000

MEDICAL REVIEW(S)

Clarification to Amendment 2 to MOR of NDA 202-895
Dec. 13, 2011

As per FAX to Applicant from the Agency regarding storage temperature reports in the EMA inspections:

- Please clarify whether any (b) (4) darunavir and ritonavir long term stability data has been generated at either (b) (4)
- In regards to darunavir/ritonavir samples from the TMC114-C228 trial that were stored at (b) (4), please provide information on the following: a) the number of trial sites and the number of subjects at each site that had darunavir/ritonavir samples stored at (b) (4), b) the total number of darunavir/ritonavir samples at each trial site that had samples stored at - (b) (4), and c) the maximum length of time

In Amendment 2 the following statement was made:
"The Applicant's response to the Division's RFI for the first question is the subject of this amendment. The Chemistry Reviewer, Dr. M Paciga, will provide an in depth review of stability and temperature issues, however his assessment indicated that based on stability data and reported temperature deviations significant changes in product quality or performance are not expected."

Clarification as per Chemistry Reviewer:

There were 2 stability/storage temperature issues identified during the clinical site inspections:

1) storage and stability of drug product (darunavir oral suspension, and possibly ritonavir) at temperatures in the range of 10-30degC; and

2) storage of blood/plasma PK samples at (b) (4) degC rather than -20degC.

It is unlikely that storage of the drug product over the range of temperatures noted (all above refrigeration or freezing) before administration to patients would adversely affect product quality or performance.

Storage of drug product at (b) (4) degC would likely impact product performance. On the other hand, storage of plasma at (b) (4) degC would not likely adversely impact chemical stability of the analytes (darunavir, metabolites).

Note: MOR #2 refers erroneously to storage at [redacted] deg and product quality/performance. As noted above plasma storage at [redacted] would not affect plasma quality not drug quality. Drug product stored at specified range of temperatures was also not affected.

Regina Alivisatos, MD

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

/s/

M R ALIVISATOS
12/13/2011

Medical Officer Review
Amendment to Review of NDA 202-895

Date	November 20, 2011
From	Regina Alivisatos, M.D.
Subject	Medical Officer Review Amendment
NDA # and Supplement #	NDA 202895/000 and SNDA 21976/S-20
Applicant	Tibotec Inc.
Date of Original Submission	March 29, 2011
Original PDUFA Goal Date	September 30, 2011
Date of Major Amendment	September 28, 2011
Revised PDUFA Date	December 30, 2011
Proprietary Name / Established (USAN) names	Prezista (darunavir)
Dosage forms / Strength	New proposed dosage form: Oral Suspension Approved dosage forms: 300 mg tablets, 150 mg tablets
Proposed Indication(s)	Treatment of HIV infection
Recommended:	Approval

This is the second amendment to the NDA package. The first, authored by the Cross Discipline Team Leader, Dr. Yodit Belew, dated September 26, 2011, had as its subject the revised dosing recommendation made by the Division for subjects weighing 10 to less than 15 kg. This recommendation was subsequently accepted by the Applicant. Specifically, the Division recommended that for subjects 3 years of age and older and weighing 10 to less than 15 kg, the dose should be calculated based on darunavir 20 mg/kg co-administered with ritonavir 3mg/kg.

Several reasons led to this change in dosing recommendation to 20/3 mg/kg instead of the Applicant's proposed (b) (4) in subjects weighing 10- <15 kg. The primary reason was the Division's assessment of a revision to the population PK analysis submitted by the Applicant to correct for an error, primarily in subjects weighing 10 - <15 kg. In this revised analysis, these subjects would have mean AUC exposure that is 53% higher that the targeted mean adults exposure value. As the lower dose did not present similar pharmacokinetic concerns and had similar efficacy and safety it was determined that this dose was the appropriate one to be included in labeling.

In addition because of concerns that the initial dosing device supplied by the Applicant could lead to dosing errors, the device was changed to an (b) (4) syringe device. Details of this device were provided in the major amendment under review including instructions for use. Both the device and the instructions are acceptable to the Division as well as to DRISK and DMEPA.

The current amendment to the MOR has been included because of the, unsolicited by the Division, submission on September 27, 2011 (SNDA 202-895/SN 41) by the Applicant of clinical sites inspection reports from the EMA for the ARIEL study (TMC114-C228). The ARIEL study was the primary pharmacokinetic and clinical study submitted in both

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