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RESEARCH**

APPLICATION NUMBER:

202895Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202895 and 21976/S-20

SUPPL #

HFD#530

Trade Name Prezista

Generic Name darunavir

Applicant Name Tibotec, Inc

Approval Date, If Known December 16, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) & 505(b)1 SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-976

Prezista Tablets

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

TMC114-C228 evaluated the pharmacokinetics and antiviral activity of twice daily dosage regimens of darunavir administered in combination with ritonavir for the treatment of HIV-1 infection in pediatric subjects 3 to less than 6 years old and weighing 10 to less than 20 kg using the darunavir oral suspension formulation.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 62477 YES ! NO
! Explain:

Investigation #2
IND # 62477 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!

YES
Explain:

! NO
! Explain:

Investigation #2

!
!

YES
Explain:

! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Linda C. Onaga, MPH
Title: Regulatory Project Manager
Date: December 16, 2011

Name of Office/Division Director signing form: Jeffrey Murray, MD, MPH
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

LINDA C ONAGA
12/16/2011

JEFFREY S MURRAY
12/16/2011

Onaga, Linda

From: Zezza, Charles [JRDUS] [CZezza@its.jnj.com]
Sent: Friday, December 16, 2011 2:26 PM
To: Onaga, Linda
Subject: RE: Prezista NDA 202895 and NDA 21976/S-20
Attachments: emfalert.txt

Linda,

We agree to the proposed changes to the Instructions for Use.

Let me know of there any additional questions.

Charles Zezza, Ph. D., MBA

J&J PRD/Tibotec Inc.
Office 908-707-3451 Cell 908-872-5723

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From: Onaga, Linda [mailto:Linda.Onaga@fda.hhs.gov]
Sent: Friday, December 16, 2011 1:56 PM
To: Zezza, Charles [JRDUS]
Subject: Prezista NDA 202895 and NDA 21976/S-20
Importance: High

Good Afternoon Charles,

We making the following the changes to the Instructions for Use for NDA 202895.

1. In Step (b) (4) "Shake the bottle well before each use" should be deleted since Step 1 describes this step.

Figure B: Opening the bottle

2. **Open the bottle of
PREZISTA Oral
Suspension.**

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LINDA C ONAGA
12/16/2011

Onaga, Linda

From: Onaga, Linda
Sent: Tuesday, December 13, 2011 2:04 PM
To: 'Zezza, Charles [JRDUS]'
Subject: NDA 202895 and NDA 21976/S-20
Attachments: DAVP PI and PPI revision for Prezista 12-13-11.doc; prezista-os-ifu-inverted DAVP revisions 12-13-11.doc

Good Afternoon Charles,

Please find attached the labeling for Prezista oral tablets, oral suspension, and instruction for use.

The Division has proposed the following changes and has the additional comment for the PI:

14 Clinical Trials

14.3 Treatment-Experienced Adult Subjects

The proportion of subjects with HIV-1 RNA less than 50 copies/mL and less than 400 copies/mL was **57.1** and **xx%**, respectively[RA1]. The mean change in CD4+ percentage from baseline was 4%. The mean change in CD4+ cell count from baseline was 109×10^6 cells/L.

[RA1]Please add in percentage for < 400 copies based on the SNAPSHOT analysis.

Instructions for Use:

1. Please add a step instructing patients to shake the bottle. This should be Step 1. An associated figure should also accompany this step. For example:

1. Shake the bottle.
 - Shake the bottle well before each use (See Figure A).
2. Open the bottle of PREZISTA Oral Suspension
 - Open the bottle by pushing downward on the cap and twisting it in the direction of the arrow (counter-clockwise) (See Figure B).

and so on.

3. Please remove the following statement within the image in Figure A ' [REDACTED] (b) (4)

2. Use a lowercase "b" in Figure G: "Closing the bottle"

The revisions are also provided in the word document attached to this email. Please provide your revision to the division by Wednesday, December 14, 2011.

Thanks,

Linda

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/s/

LINDA C ONAGA
12/13/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: December 8, 2011

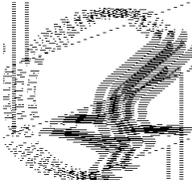
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec, Inc.	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-3979
Subject: NDA 202895-Labeling Comments	

Total number of pages including cover: 10

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895
21-976/S-20

Drug: Prezista (darunavir) oral suspension
Prezista (darunavir) tablets

Date: December 8, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, M.P.H., Regulatory Project Manager

Concur: Yodit Belew, M.D., Acting Clinical Team Leader
Regina Alivisatos, M.D., Clinical Reviewer
Stanley Au, PharmD, Clinical Pharmacology Reviewer
Sarah Robertson, PharmD, Clinical Pharmacology Team Leader

Subject: NDA 202895-Labeling Comments

Please reference your submissions dated November 30, 2011. The following comments are being conveyed on behalf of the review team for your application.

I. Package Insert

1. Clinical Pharmacology:

In Table 11, for the new footnote that was added stating "(b) (4)", please clarify if the footnote is meant to convey that the same subjects may be included in both the 10 kg to <15 weight group and the 15 kg to < 20 kg weight group. If yes, please modify the footnote to state "Subjects may have contributed PK data to both the 10 kg to < 15 kg weight group and the 15 kg to < 20 kg weight group".

2. Section 17

The first paragraph of the subsection should be revised as follows:

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (Patient Information)]

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with PREZISTA.** A Patient Package Insert for PREZISTA is available for patient information.

17.1 Information About Therapy with PREZISTA

Patients should be informed that PREZISTA is not a cure for HIV infection. Patients should stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using PREZISTA. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to share personal items that can have blood or body fluids on them, like toothbrushes and razor blades. Patients should be advised never to re-use or share needles.

II. Patient Package Insert

The following should be revised as follows:



Patients must stay on continuous HIV therapy to control infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV infection.

- Do not share needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never re-use or share needles.

Ask your healthcare provider if you have any questions on how to prevent passing HIV to other people.

HOW SHOULD I TAKE PREZISTA?

- Take PREZISTA every day exactly as prescribed by your healthcare provider.
- You must take ritonavir (NORVIR[®]) at the same time as PREZISTA.
- Do not change your dose of PREZISTA or stop treatment without talking to your healthcare provider first.
- Take PREZISTA and ritonavir (NORVIR[®]) with food.
- Swallow PREZISTA tablets whole with a drink. If you have difficulty swallowing PREZISTA tablets, PREZISTA oral suspension is also available. Your health care provider will help determine whether PREZISTA tablets or oral suspension is right for you.
- PREZISTA oral suspension should be given with the supplied oral dosing syringe. Shake the suspension well before each usage.
- If your child is taking PREZISTA, your child's healthcare provider will decide the right dose based on your child's weight. Your child's healthcare provider will tell you how much PREZISTA (tablets or oral suspension) and how much ritonavir (NORVIR[®]) (capsules, tablets or solution) your child should take. Your child should take PREZISTA with ritonavir twice a day with food. If your child does not tolerate ritonavir oral solution, ask your child's healthcare provider for advice.
- [If you take too much PREZISTA, call your healthcare provider or go to the nearest hospital emergency room right away.](#)

III. Instructions for Use.

Please see attached for additional comments from the Division of Medical Policy, Patient Labeling Team.

Please provide your revisions to the Agency by **Monday, December 12, 2011**.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
12/08/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: November 17, 2011

To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec, Inc.	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-3979

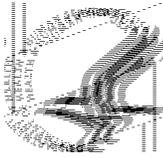
Subject: NDA 202895-Labeling Comments

Total number of pages including cover: 7

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895
21-976/S-20

Drug: Prezista (darunavir) oral suspension
Prezista (darunavir) tablets

Date: November 17, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, M.P.H., Regulatory Project Manager

Concur: Yodit Belew, M.D., Acting Clinical Team Leader
Regina Alivisatos, M.D., Clinical Reviewer
Stanley Au, PharmD, Clinical Pharmacology Reviewer
Sarah Robertson, PharmD, Clinical Pharmacology Team Leader

Subject: NDA 202895-Labeling Comments

Please reference your submissions dated November 9, 2011. The following comments are being conveyed on behalf of the review team for your application.

After a review of the EMA inspection reports for selected pediatric trial sites that were submitted on September 28, 2011 and your responses that were submitted on November 9, 2011, DAVP recommends that the PK and antiviral activity data for the TMC114-C228 trial should exclude all information obtained from the site where Dr. Robert Kimutai was the principal investigator.

- 1) Using the draft label that was submitted on September 28, 2011, please exclude the subjects that were enrolled at the Kimutai site from the following data:

A) Pharmacokinetic data:

1. Please specify how many additional subjects are excluded from the AUC (0-24h) and C_{0h} estimates in Table 11 for the 10 kg to less than 15 kg group

DAVP/HFD-530 • 10903 New Hampshire Ave • Silver Spring, MD 20903 • (301) 796-1500 • Fax (301) 796-9883

(receiving 20 mg/kg twice daily of darunavir) and/or the 15 to less than 20 kg group (receiving 380 mg twice daily of darunavir).

2. If necessary, please revise the AUC (0-24h) and C_{0h} estimates in Table 11 for the 10 kg to less than 15 kg and/or the 15 to less than 20 kg groups.

B) Clinical data:

1. Provide a revised efficacy analyses using the snapshot algorithm, excluding subjects enrolled from the Kenyan site.
 2. The updated label should reflect the new total number of pediatric subjects enrolled in trial TMC114-C228 (i.e. after the exclusion of subjects from the Kenyan site) and all the relevant sections or subsections should be updated accordingly.
- 2) Please clarify the following issue for the PK analysis in Table 18 for the TMC114-C228 report:
- A) For the week 2 PK analysis for darunavir/ritonavir 20 mg/kg and 3 mg/kg twice daily dosing (prior to dose adjustment), was the PK data revised subsequent to the correction of body weights for Visit 105 OR after excluding the subjects that were enrolled at the Kimutai site? If yes, please submit a revised summary table.
 - 3) For the submission dated September 9, 2011, subsequent to the addition of subject #21 as part of the population PK data for the 15 kg to < 20 kg group and excluding the subjects that were enrolled at the Kimutai site, please clarify if Table 2, Table 3, Table 4, and Table 5 or Appendix 1, 2, 3 and 4 need to be updated. If yes, please submit the revised summary tables, figures or listings.

Instructions For Use:

Please see attached additional comments from the Division of Risk Management.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
11/17/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: October 6, 2011

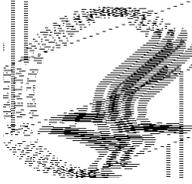
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec, Inc.	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-3979
Subject: NDA 202895-Labeling Comments	

Total number of pages including cover: 7

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895
21-976/S-20

Drug: Prezista (darunavir) oral suspension
Prezista (darunavir) tablets

Date: October 6, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, M.P.H., Regulatory Project Manager

Concur: Yodit Belew, M.D., Acting Clinical Team Leader
Regina Alivisatos, M.D., Clinical Reviewer
Stanley Au, PharmD, Clinical Pharmacology Reviewer
Sarah Robertson, PharmD, Clinical Pharmacology Team Leader

Subject: NDA 202895-Labeling Comments

Please reference your submissions dated September 14 and 28, 2011. The following comments are being conveyed on behalf of the review team for your application.

September 14, 2011 SN 35

1. Please see attached edits to the Instructions for use from the Division of Risk Management.

September 28, 2011 SN 40

Division of Medication Error Prevention and Risk Management (DMEPA)
comments:

- A. Carton

1. Delete the statement [REDACTED] (b) (4) from the principal display panel of the carton labeling since it adds clutter and is duplicative information.
2. Revise the statement [REDACTED] (b) (4) to read "For Use Only With Prezista Oral Suspension". Ensure "For Oral Use Only" immediately precedes "With Prezista Oral Suspension". Please see the attached diagram for the recommended placement and layout of the statement.

September 28, 2011 SN 41:

1. Provide a copy of your assessment to the inspection reports issued by the EMA (CHMP). In addition, submit your rationale for using/accepting the data from the three sites inspected in support of pediatric labeling for children 3 to <6 years of age.
2. Please clarify whether any [REDACTED] (b) (4) C darunavir and ritonavir long term stability data has been generated at either [REDACTED] (b) (4) or at [REDACTED] (b) (4).
3. In regards to darunavir/ritonavir samples from the TMC114-C228 trial that were stored at [REDACTED] (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 [REDACTED] (b) (4), b) the total number of darunavir/ritonavir samples at each trial site that had samples stored at [REDACTED] (b) (4) and c) the maximum length of time that darunavir/ritonavir samples were stored at [REDACTED] (b) (4) at each site.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LINDA C ONAGA
10/06/2011



NDA 202895

**REVIEW EXTENSION
MAJOR AMENDMENT**

Tibotec, Inc.
Attention: Charles Zezza, PhD, MBA
Director, Global Regulatory Affairs
920 Route US Highway 202S
PO Box 300
Raritan, NJ 08869

Dear Dr. Zezza:

Please refer to your March 29, 2011 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prezista® (darunavir) oral suspension 100 mg/mL.

On September 28, 2011, we received your September 28, 2011 unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 30, 2011.

In addition, in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012," the timeline for communicating labeling changes and/or postmarketing requirements/commitments, provided in our May 25, 2011 filing communication letter, have already been met and no new timeline will be provided.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager, at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KENDALL A MARCUS
09/30/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: September 26, 2011

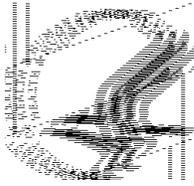
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec, Inc.	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-3979
Subject: NDA 202895-Labeling Comments 4	

Total number of pages including cover: 5

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: September 26, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, M.P.H., Regulatory Project Manager

Concur: Yodit Belew, M.D., Acting Clinical Team Leader
Regina Alivisatos, M.D., Clinical Reviewer
Sarah Robertson, PharmD, Clinical Pharmacology Team Leader

Subject: NDA 202895-Labeling Comments

Please reference your submissions dated September 22 and 23, 2011. The following comments are being conveyed on behalf of the review team for your application.

September 22, 2011 SN 37

Division of Medication Error Prevention and Risk Management (DMEPA) comments:

A. Oral Dosing Syringe

1. The sample oral syringes provided to the Agency on September 22, 2011 do not match the graphic presentation of the syringe submitted on the same date. Our comments are applicable to the graphic presentation of the syringe. Please submit a graphic of the revised syringe that incorporates the recommendations below as soon as possible. Additionally, provide the Agency with the revised syringes as soon as they are available.
 - a. Delete the dosage unit “mL” from its current position between the numbers 5 and 6. Place the dosage unit “mL” beside each numerical unit (e.g., 2 mL, 3 mL, etc.).

- b. Replace the statements (b) (4) with one statement to read:

For Oral Use Only
With Prezista Suspension

Use the same font type and size for the entire statement.

September 23, 2011 SN 38:

Thank you for your response regarding the final dose recommendation for pediatric patients 3 years of age or older and weighing 10 to <15 kg. We have reviewed and considered your response.

However, after considering the pharmacokinetic data, pharmacodynamic relationship (exposure-response) and the patient population (3 years of age and older weighing 10 to <15 kg), the Division continues to believe darunavir 20 mg/kg co-administered with ritonavir 3mg/kg is the most appropriate dose selection for this population.

For the teleconference scheduled for Tuesday, September 27, 2011, we plan to discuss the following:

1. The pharmacokinetics data: targeted adult AUC value (80% - 130% of the mean adult AUC value) and the observed exposures with 20/3 mg/kg vs. 25/3 mg/kg
2. Pharmacodynamics: lack of exposure-response evidence supporting higher exposure in pediatrics patients than adults
3. Safety data: small number of subjects providing conclusive safety information at the 25/3mg/kg dose
4. Patient population: age group and PI resistance

In addition, please update the following sections in the label:

Section 2 Dosage and Administration (2.2)

Section 12 Clinical Pharmacology (12.3)

When presenting the PK estimates in Table 11, please split the two pediatric weight bands (10 to <15 kg and 15 to <20 kg) and present the result separately for each. For the 10 to <15 kg cohort (n=10), include the population PK parameter estimates based on the Weeks 2 and 4 analysis that evaluated a darunavir dose of 20 mg/kg twice daily. For the 15 to <20 kg cohort (n=14), include the population PK parameter estimates based on the Visit 105 and Week 24 analysis that evaluated a darunavir dose of 380 mg twice daily. In addition, because subject #21 weighed 15 kg and received 380 mg twice daily after adjustment of the darunavir dosage regimen, we recommend that the subject also be included in the population PK data for the 15 to < 20 kg group (for a revised total number of 15 subjects). Please include footnotes indicating the respective weeks or visits that the population PK data is derived from for each weight group. Also, in addition to the median values and ranges, please add means and standard deviations, as displayed in Table 10.

Please provide the Division with your revised label and syringe graphics no later than **12:00 noon EST, Wednesday, September 28, 2011.**

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
09/26/2011



Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF ANTIMICROBIAL PRODUCTS

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: September 16, 2011

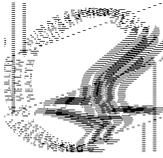
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 and 21-976/S-20 Labeling Comments 3	

Total number of pages including cover: 94

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: September 16, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202895 and NDA 21-976/S-20 Labeling Comments 3

The attached Microsoft WORD Document was sent to the Sponsor on September 16, 2011 and incorporated labeling comments for NDA 202895 (Prezista[®] oral suspension) and NDA 21-976 S-20 (Prezista[®] tablets). The submission date of the revised labeling was September 12, 2011.

Please provide the Division with your response no later than Wednesday, **September 21, 2011.**

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
09/16/2011

Onaga, Linda

From: Onaga, Linda
Sent: Thursday, September 15, 2011 11:38 AM
To: 'Zezza, Charles [JRDUS]'
Subject: NDA 202895

Charles,

I apologize for this piecemeal request for the new syringe.

Please submit the following information:

- 4 samples of the alternative syringe
- 2 adaptors that will be used for the bottle
- 2 bottles of the actual drug product
- 1 copy of the graphics/proposed labeling for the syringe.

Please note the Division refers the alternate as a syringe. Please update the labeling to reflect this.

As you did before, please submit a letter to the NDA stating the information sent to the division and send the graphics/proposed labeling through the gateway as well.

Once again I apologize for this.

Thanks

Linda

*Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6321
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.0759
Fax: 301.796.9883
Email: linda.onaga@fda.hhs.gov*

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/s/

LINDA C ONAGA
09/21/2011

Onaga, Linda

From: Onaga, Linda
Sent: Tuesday, September 13, 2011 8:52 AM
To: 'Zezza, Charles [JRDUS]'
Subject: NDA 202895 Follow-up IR
Importance: High

Good Morning Charles,

DMEPA request the following for NDA 202895:

- Please Submit an updated instructions for use for the alternate dosing device that includes directions on how to place the adaptor in the bottle neck.

Please submit this information by Wednesday, September 14, 2011.

Thanks

Linda

*Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6321
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.0759
Fax: 301.796.9883
Email: linda.onaga@fda.hhs.gov*

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/s/

LINDA C ONAGA
09/21/2011

David, Jeannie C

From: Zezza, Charles [JRDUS] [CZezza@its.jnj.com]
Sent: Tuesday, September 13, 2011 9:58 AM
To: David, Jeannie C
Cc: Onaga, Linda
Subject: RE: Teleconferences - Aug 26 (b) (4) meeting
Follow Up Flag: Follow up
Flag Status: Red
Attachments: emfinfo.txt

Jeannie,

Message received. I have shared with the team.

Charles Zezza, Ph. D., MBA

Tibotec/J&JPRD
Office 908-707-3451 Cell 908-872-5723

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From: David, Jeannie C [mailto:Jeannie.David@fda.hhs.gov]
Sent: Monday, September 12, 2011 2:02 PM
To: Zezza, Charles [JRDUS]
Cc: Onaga, Linda
Subject: RE: Teleconferences - Aug 26 (b) (4) meeting
Importance: High

Hi Charles,

We have the following CMC request:

Provide information on dosing accuracy of the alternative oral syringe (no (b) (4)). We recommend these studies use the oral suspension at 0.2 mL increments across the dosing range. Please note, the information supplied on September 9, 2011 was for the original dosing (b) (4) (no. (b) (4)).

Please provide Tibotec's response by September 14, 2011. Kindly confirm receipt of this email.

Regards,

Jeannie

Jeannie David, MS
Regulatory Health Project Manager
CDER/OPS/ONDQA
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 1475

Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877
jeannie.david@fda.hhs.gov

From: Zezza, Charles [JRDUS] [mailto:CZezza@its.jnj.com]
Sent: Friday, September 02, 2011 1:29 PM
To: Onaga, Linda; David, Jeannie C
Subject: RE: Teleconferences - Aug 26 (b) (4) meeting

Linda,

We have been following up on the issue of the (b) (4) and have looked at possible alternatives. We will be able to provide a response to this issue on Friday 09 Sept 2011.

Please let me know if there are any questions.

Best regards

Charles Zezza, Ph. D., MBA
Tibotec/J&JPRD
Office 908-707-3451 Cell 908-872-5723

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From: Onaga, Linda [mailto:Linda.Onaga@fda.hhs.gov]
Sent: Wednesday, August 31, 2011 9:41 AM
To: Zezza, Charles [JRDUS]; David, Jeannie C
Subject: RE: Teleconferences - Aug 26 and Aug 30 - List of Attendees

Good Morning Charles,

The following FDA representatives participated on o the Aug 26th (b) (4) discussion:

Jeffrey Murray, MD, Deputy Director
Yodit Belew, MD, Acting Clinical Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Mark Seggel, PhD, CMC Reviewer
Rapti Madurawe, PhD, ONDQA Branch Chief
Jeannie David, MS, ONDQA RPM
Loretta Holmes, PharmD, DEMPA Reviewer
Zach Oleszczuk, PharmD, DEMPA Team Leader
Linda Onaga, MPH, RPM

Jeannie will provide the names for yesterday's T-con.

Linda

From: Zezza, Charles [JRDUS] [mailto:CZezza@its.jnj.com]
Sent: Wednesday, August 31, 2011 9:16 AM
To: David, Jeannie C; Onaga, Linda
Subject: Teleconferences - Aug 26 and Aug 30 - List of Attendees

Jeannie,

Just a note to ask for confirmation of the FDA attendees for the Aug 26th meeting and the Aug 30th meeting.

From our side the attendees were:

Aug 26 ((b) (4) discussion)

Goedele De Smedt	Compound Development Team Leader
Frank Tomaka	Clinical Leader
Thomas Kakuda	Clinical Pharmacology Leader
Annemie Hendrickx	Clinical Operations Leader
Koen Iterbeke	Chem-Pharm Development Leader
Tom Pituk	Global CMC Regulatory Affairs
Esmerald Hermans	Packaging Engineer
Robin Keen	Vice President – Regulatory Affairs
Paul Imm	Global Labeling
Rhonda Hatfield	Regulatory Affairs
Charles Zezza	North American Regulatory Leader

Aug 30 (dissolution specification)

Frank Tomaka	Clinical Leader
Thomas Kakuda	Clinical Pharmacology Leader
Koen Iterbeke	Chem-Pharm Development Leader
Tom Pituk	Global CMC Regulatory Affairs
Jyh-Ming Shoung	Non-Clinical Biostatistics
Charles Zezza	North American Regulatory Leader

Best regards

Charles Zezza, Ph. D., MBA
Tibotec/J&JPRD
Office 908-707-3451 Cell 908-872-5723

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/s/

JEANNIE C DAVID
09/13/2011

Onaga, Linda

From: Onaga, Linda
Sent: Tuesday, September 13, 2011 8:52 AM
To: 'Zeza, Charles [JRDUS]'
Subject: NDA 202895 Follow-up IR
Importance: High

Good Morning Charles,

DMEPA request the following for NDA 202895:

- Please Submit an updated instructions for use for the alternate dosing device that includes directions on how to place the adaptor in the bottle neck.

Please submit this information by Wednesday, September 14, 2011.

Thanks

Linda

*Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6321
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.0759
Fax: 301.796.9883
Email: linda.onaga@fda.hhs.gov*

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/s/

LINDA C ONAGA
09/13/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: September 12, 2011

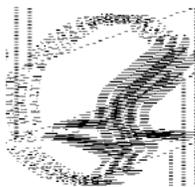
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec, Inc.	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-3979
Subject: NDA 202895-Carton and Container Comments	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: September 12, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, M.P.H., Regulatory Project Manager

Concur: Yodit Belew, MD, Acting Team Leader
Regina Alivisatos, M.D., Clinical Reviewer

Subject: NDA 202895-Labeling Comments (SN 30 and 32)

Please reference your submissions dated September 9, 2011. The following from the Division of Medication Error Prevention and Risk Management (DMEPA) comments is being conveyed on behalf of the review team for your application.

Container label:

1. The background color for the previously submitted label was (b) (4). However, the background color on the revised label appears to be (b) (4). Please clarify if this was an intended change to the container label.

Syringe:

2. In the draft instructions for use for the alternative dosing device submitted on September 9, 2011, the second direction instructs the patient to (b) (4). Please clarify how patients will be able to determine the adaptor is properly (b) (4). Will there be an audible click or other indicator that the patient should be looking for?
3. Submit detailed diagrams of both proposed devices (up close view) that could be included in the instructions for use that will show the details of the graduation marks noted on the devices.

Please provide the Division with your response no later than *Wednesday, September 14, 2011*.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
09/12/2011

David, Jeannie C

From: Zezza, Charles [JRDUS] [CZezza@its.jnj.com]
Sent: Friday, September 09, 2011 2:08 PM
To: David, Jeannie C; Onaga, Linda
Subject: RE: NDA 202-895 - Text for response
Attachments: NDA 202-895 Seq 0031 Cover Letter.pdf; emfinfo.txt

Dear Jeannie and Linda,

Please note that we provided the PMC and the updated specifications to NDA 202-895 this afternoon (sequence 0031). Please see attached cover letter for your review.

Let me know if there are any questions.

Charles Zezza, Ph. D., MBA

Tibotec/J&JPRD
Office 908-707-3451 Cell 908-872-5723

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From: David, Jeannie C [mailto:Jeannie.David@fda.hhs.gov]
Sent: Friday, September 02, 2011 4:27 PM
To: Zezza, Charles [JRDUS]
Cc: Onaga, Linda
Subject: RE: NDA 202-895 - Text for response

Hi Charles,

I'm sure you noticed, but there was an inadvertent misplacement of the bullet. Here is the correct version:

We agree to a Phase IV Post-Marketing Commitment (PMC) with the objective of providing the additional dissolution data from full-scale manufactured batches that are needed for the setting of the final regulatory dissolution specification.

Specifically, we agree to collect dissolution profile data from all available full-scale manufactured batches, during the first 12 months after approval of the NDA. The collection of dissolution data will target the dissolution specification recommended by the FDA (see bullet below) and will include dissolution testing at Stage 1, 2, or 3 as appropriate.

- **Q = (b) (4) % at 30 minutes**

(b) (4)

Thanks,

Jeannie

Jeannie David, MS
Regulatory Health Project Manager
CDER/OPS/ONDQA
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 1475
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877
jeannie.david@fda.hhs.gov

From: Zezza, Charles [JRDUS] [mailto:CZezza@its.jnj.com]
Sent: Friday, September 02, 2011 4:06 PM
To: David, Jeannie C
Cc: Onaga, Linda
Subject: RE: NDA 202-895 - Text for response

Jeannie,

Many thanks. I will share with the team and prepare an amendment.

Best regards

Charles Zezza, Ph. D., MBA
Tibotec/J&JPRD
Office 908-707-3451 Cell 908-872-5723

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From: David, Jeannie C [mailto:Jeannie.David@fda.hhs.gov]
Sent: Friday, September 02, 2011 3:46 PM
To: Zezza, Charles [JRDUS]
Cc: Onaga, Linda
Subject: RE: NDA 202-895 - Text for response

Dr. Zezza,

We suggest that the following be submitted as an amendment to the NDA, in order to outline Tibotec's agreement to a post-marketing commitment, as we discussed in our August 30, 2011, teleconference meeting. General language based on the language below will be included in the final approval letter for the NDA.

We agree to a Phase IV Post-Marketing Commitment (PMC) with the objective of providing the additional dissolution data from full-scale manufactured batches that are needed for the setting of the final regulatory dissolution specification.

- Q = (b) (4) % at 30 minutes

Specifically, we agree to collect dissolution profile data from all available full-scale manufactured batches, during the first 12 months after approval of the NDA. The collection of dissolution data will target the dissolution specification recommended by the FDA (see bullet below) and will include dissolution testing at Stage 1, 2, or 3 as appropriate.

(b) (4)

Please let me know if there are any questions.

Best regards,

Jeannie

Jeannie David, MS
Regulatory Health Project Manager
CDER/OPS/ONDQA
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 1475
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877
jeannie.david@fda.hhs.gov

From: Zezza, Charles [JRDUS] [mailto:CZezza@its.jnj.com]
Sent: Thursday, September 01, 2011 2:20 PM
To: David, Jeannie C
Subject: NDA 202-895 - Text for response

Jeannie,

Please let me know if you have any text to share with me regarding the dissolution discussion we had on Tuesday so I can prepare the team and a response.

You can reach me on my cell 908 872 5723.

Best regards

Charles Zezza, Ph. D., MBA
Tibotec/J&JPRD
Office 908-707-3451 Cell 908-872-5723

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/s/

JEANNIE C DAVID
09/13/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 1 OFFICE OF ANTIMICROBIAL
 PRODUCTS

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: September 8, 2011

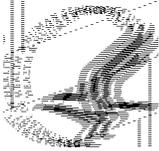
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 and 21-976/S-20 Labeling Comments 2	

Total number of pages including cover: 94

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: July 27, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202895 and NDA 21-976/S-20 Labeling Comments 2

The attached Microsoft WORD Document was sent to the Sponsor on September 8, 2011 and incorporated labeling comments for NDA 202895 (Prezista[®] oral suspension) and NDA 21-976 S-20 (Prezista[®] tablets). The submission date of the revised labeling was August 4, 2011.

Please provide the Division with your response no later than Monday, **September 12, 2011**.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

72 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LINDA C ONAGA
09/08/2011



INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Tibotec, Inc
Attention: Charles Zezza, Ph.D., M.B.A.
Director, Global Regulatory Affairs
920 Route US Highway 202S
PO Box 300
Raritan, NJ 08869

Dear Dr. Zezza:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREZISTA[®] (darunavir) tablets and oral suspension.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4)¹. The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented (b) (4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

¹ These violations include studies conducted by (b) (4) specific to the (b) (4) facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] ^{(b) (4)} during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call me at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
09/01/2011

Onaga, Linda

From: Onaga, Linda
Sent: Thursday, August 25, 2011 12:45 PM
To: 'Zezza, Charles [JRDUS]'
Subject: NDA 202895

Charles,

Please see below follow up emails regarding NDA 202895 from the clinical pharmacology reviewer. Please respond within one week and no later than September 1, 2011.

As a follow up to the Clinical Pharmacology information that was submitted on August 18 and 19, 2011, please provide further information on the following items:

1) The population PK analysis for visit 105 that was included as part of the DSMB meeting minutes for June 30, 2010 included the following AUC(0-12h) information for visit 105: a) Overall mean: 77.3 mcg*hr/mL (n=18), b) Mean (< 15 kg): 88.4 mcg*hr/mL [n=8], and c) Mean: ≥ 15 kg: 68.3 mcg*hr/mL [n=10].

However, the visit 105 population PK analysis data obtained from the week 24 analysis that was submitted on August 18, 2011 reported different mean pharmacokinetic data for AUC(0-12h) and C_{0h} and included data from 4 children weighing 10 kg to < 15 kg and from 14 children weighing ≥15 kg. Please explain the differences in the reported mean pharmacokinetic data for AUC(0-12h) and C_{0h} and the number of children included in the subgroup analysis for children weighing 10 kg to < 15 kg and ≥15 kg.

2) Please clarify whether the overall AUC(0-12h) or the AUC(0-12h) values for children weighing 10 kg to < 15 kg and ≥15 kg were used in determining whether the target exposure within 80%-130% of 62.3 mcg*hr/mL was achieved when the PK data obtained at week 2 or 2 weeks after dosage adjustment was evaluated.

3) Regarding the subjects that were excluded from Table 23 in the TMC114-C228 trial report, please clarify whether subject 42 was also excluded from the visit 3 population PK analysis because there were no blood samples drawn for pharmacokinetic analysis at week 2 (the table that was submitted on August 18, 2011 only reports the exclusion of week 4 PK data) and therefore subjects 5, 10, 14, 18, 33, 38, 42 and 30 were the eight subjects excluded from Table 23 out of 27 subjects.

4) Please confirm that subjects 26, 33, 38 and 30 were the four subjects excluded from Table 24 in the TMC114-C228 trial report out of 27 subjects.

5) Addendum 2 for the (b) (4) darunavir/ritonavir method validation report (in section 2.1, Appendices 2 and 3) and Appendix 6 (Study Plan and amendment number 1) cite different batches and expiration dates for the darunavir reference standards and different expiration dates for the ritonavir reference standard. Please clarify this discrepancy. If the reference standards in Addendum 2, section 2.1 were used, please specify the dates the darunavir and ritonavir stock solutions were prepared.

6) For the TMC114-C228 trial, please confirm that analytical batches AN 10-1 to AN 10-12 were analyzed using the original method with a calibration curve range of 5 to 5,000 ng/mL.

Thanks

Linda

Linda C. Onaga, MPH
 Regulatory Project Manager
 Division of Antiviral Products (DAVP)

FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6321
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.0759
Fax: 301.796.9883
Email: linda.onaga@fda.hhs.gov

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/s/

LINDA C ONAGA
09/07/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: August 16, 2011

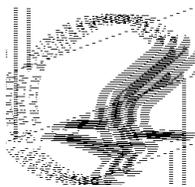
To: Charles Zezza, PhD MBA	From: Robert G. Kosko, Jr., Pharm.D., M.P.H.
Company: Tibotec, Inc.	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-3979
Subject: NDA 202895-Comment for August 4, 2011 Submission	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: August 16, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Robert G. Kosko, Jr., Pharm.D., M.P.H., Regulatory Project Manager

Subject: NDA 202895-Comment for August 4, 2011 Submission

Please reference your submissions dated August 4, 2011. The following comment is being conveyed on behalf of the review team for your application.

Please submit the calculations that were performed to support the proposed 3-fold AUC values for the rat in section 8.1 of your draft label.

Please provide the Division with your response no later than ***Monday, August 22, 2011.***

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-3979 if you have any questions regarding the contents of this transmission.

Robert G. Kosko, Jr., Pharm.D., M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Robert G Kosko
08/16/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: August 11, 2011

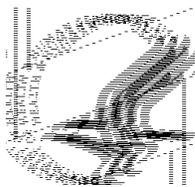
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: August 11, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202895

Please reference your submission dated March 30, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) For the TMC114-C228 trial, please specify how many pediatric subjects weighing between 15 kg to < 20 kg received darunavir tablets after week 24. For subjects weighing 15 kg to < 20 kg who received darunavir tablets after week 24, please also specify how many of these subjects had (or are anticipated to have) week 48 PK data while on the tablet. Of these subjects, how many have weights that increased to 20 kg or greater before week 48.
- 2) Please provide the descriptive statistics for the population PK data (similar to Table 18 in the TMC114-C228 trial report) that was analyzed for subjects two weeks after dose adjustment receiving darunavir 25 mg/kg when combined with ritonavir 3 mg/kg (10 kg to < 15 kg) or 375 mg/50 mg twice daily (15 kg to < 20 kg). The data should be presented in two versions: including subjects 5, 10, 14 and 18 and excluding subjects 5, 10, 14 and 18.

- 3) Please clarify the following: Out of the twenty seven subjects that were enrolled in the TMC114-C228 trial, please clarify which subjects were excluded from the following population PK analysis and the reasons for excluding the subjects from the analysis:
- a) At week 2, prior to dose adjustment, for subjects receiving darunavir 20 mg/kg when combined with ritonavir 3 mg/kg twice daily (24 subjects included in Table 18 in the TMC114-C228 trial report).
 - b) Two weeks after dose adjustment, for subjects receiving darunavir 25 mg/kg when combined with ritonavir 3 mg/kg (10 kg to < 15 kg) or 375 mg/50 mg twice daily (15 kg to < 20 kg).
 - c) The summary statistics for Table 23 in the TMC114-C228 trial report (19 subjects included in Table 23).
 - d) The summary statistics for Table 24 in the TMC114-C228 trial report (23 subjects included in Table 24).
- 4) For Tables 23 and 24, please clarify which of the visits are included in each of the tables. For example, is population PK data from weeks 2 and 4 included in Table 23 and PK data from weeks 24 and visit 105 included in Table 24?
- 5) For the plasma concentrations that are reported in the current submission from the TMC114-C228 trial, please clarify whether there were any plasma samples that were analyzed using the modified method with a lower limit of quantification of 5 ng/mL and an upper limit of quantification of 10000 ng/mL.

Please provide the Division with your response no later than **Thursday, August 18, 2011**.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
08/11/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: August 3, 2011

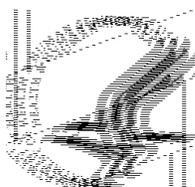
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: August 3, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202895

Please reference your submission dated March 30, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) For each darunavir tablet formulation below, please confirm that the information regarding the current or previously US marketed darunavir tablets is accurate, including the specific formulation that is cited:
 - A) 75 mg tablet (Current US marketed formulation: F029)-biowaiver granted
 - B) 150 mg tablet (Current US marketed formulation: F050)-biowaiver granted
 - C) 400 mg tablet (Current US marketed formulation: F030)-biowaiver granted
 - D) 600 mg tablet (Current US marketed formulation: F032) bioequivalence established under fasted conditions with the formerly US marketed 300 mg tablets (F016)

Please provide the Division with your response no later than Wednesday, August 10, 2011.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
08/03/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: July 27, 2011

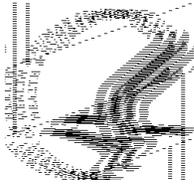
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: July 27, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Subject: NDA 202895

Please reference your submissions dated March 30, 2011. The following comments are being conveyed on behalf of Division of Medication Error Prevention and Analysis (DMEPA) for your application.

- 1) Please submit both the front and back view of the (b) (4), including any and all graphics that they intend to be on the final marketed version
- 2) Please clarify whether or not any of the graphics will be in color, or whether all graphics will be in black font.

Please provide the Division with your response no later than **Friday, July 29, 2011**.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
07/27/2011



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: July 27, 2011

To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759

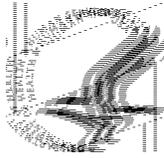
Subject: NDA 202895 and 21-976/S-20 Labeling Comments 1

Total number of pages including cover: 94

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: July 27, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202895 and NDA 21-976/S-20 Labeling Comments 1

The attached Microsoft WORD Document was sent to the Sponsor on July 20, 2011 and incorporated labeling comments for NDA 202895 (Prezista[®] oral suspension) and NDA 21-976 S-20 (Prezista[®] tablets). The submission date of the revised labeling was June 10, 2011.

Please provide the Division with your response no later than **Thursday, August 4, 2011**.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE**. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
07/27/2011



NDA 202-895

INFORMATION REQUEST

Tibotec, Inc.
Attention: Charles Zezza, Ph.D., M.B.A.
Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Dr. Zezza:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prezista (darunavir) Suspension, 100 mg/ml.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. In order to continue our evaluation of your NDA, we request your response by August 19, 2011.

1. Please provide dosing accuracy data, obtained with darunavir oral suspension, for the dosing syringe over the range of 2 mL to 6 mL.
2. Please comment on the time-scale for interconversion of the ethanolate to the hydrate in an aqueous environment. In addition, please summarize any potential impact of the interconversion on product performance.
3. Please indicate the maximum validated bulk holding time, without (b) (4) (3.2.P.2.3.1.4.10), prior to (b) (4) and initiation of the filling process.
4. As proposed, the drug product specification does not include several tests that are routinely applied to suspensions in order to provide assurance of batch to batch consistency and performance. Please add the following tests, or provide further justification and risk assessment, including available data obtained at release and on stability, for omitting them:
 - a. content uniformity (inter-bottle);
 - b. particle size distribution; and
 - c. viscosity.
5. The proposed test for resuspendability is based solely on visual assessment of homogeneity. We previously noted in our Information Request letter dated July 8, 2011, that the time required to resuspend the drug product should be defined. Please provide

any available assay data obtained on samples taken from the top and bottom of bottles after shaking for the specified period of time. Please justify the visual assessment of homogeneity rather than by an HPLC assay.

If you have any questions, contact Jeannie David, Regulatory Project Manager, at (301) 796-4247, or jeannie.david@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN P MILLER
07/27/2011
For Rapti Madurawe

David, Jeannie C

From: David, Jeannie C
Sent: Friday, July 15, 2011 4:04 PM
To: 'Zezza, Charles [JRDUS]'
Cc: Onaga, Linda
Subject: RE: PREZISTA NDA 202-895
Attachments: NDA 202-895 Syringe Graphics.pdf

Dr. Zezza,

Thank you for providing the information. We still request samples of the final syringes, as soon as they become available around the week of August 22. Please send 4 samples.

Regards,

Jeannie

Jeannie David, MS
Regulatory Health Project Manager
CDER/OPS/ONDQA
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 1475
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877
jeannie.david@fda.hhs.gov

From: Zezza, Charles [JRDUS] [<mailto:CZezza@its.jnj.com>]
Sent: Friday, July 15, 2011 3:43 PM
To: David, Jeannie C
Subject: RE: PREZISTA NDA 202-895

Jeannie,

As a follow-up to the question on the final syringe samples request, please note that the final order has not been placed with the vendor.

An order can be placed to have the syringes available at the plant in Belgium around the week of August 22 if required. These syringes would be similar in construction to the samples I provided earlier with the exception of the graphics on the barrel of the syringe.

I have attached the final pdf version of the graphics that will be included on the final syringe.

Please let me know if this adequately addresses your needs and there is no further need for a final syringe.

Let me know if you have any questions.

Charles Zezza, Ph. D., MBA

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From: David, Jeannie C [mailto:Jeannie.David@fda.hhs.gov]
Sent: Tuesday, July 12, 2011 9:15 AM
To: Zezza, Charles [JRDUS]
Cc: Onaga, Linda
Subject: RE: PREZISTA Support
Importance: High

Dr. Zezza:

Please see the attached electronic courtesy copy of an CMC Information Request letter, signed on July 8, 2011. Please confirm receipt of this letter. We kindly request Tibotec's response by July 29, 2011.

Do you know when the final syringe samples will arrive to me? We request 2 final samples to fulfill our May 25, 2011, request.

Regards,

Jeannie

Jeannie David, MS
Regulatory Health Project Manager
CDER/OPS/ONDQA
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 1475
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877
jeannie.david@fda.hhs.gov

From: Zezza, Charles [PRDUS] [mailto:CZezza@its.jnj.com]
Sent: Friday, June 10, 2011 4:18 PM
To: David, Jeannie C
Cc: Onaga, Linda
Subject: RE: PREZISTA Support

Jeannie,

The response to the 25 May 2011 questions are on track for 15 June 2011.

I will confirm with the supply group in Belgium when the final syringe samples will be available. Please note that June 13th is a holiday so I may not have a response until Tues/Wed next week.

Best regards

Charles Zezza, Ph. D., MBA

Tibotec/J&JPRD
Office 908-707-3451 Cell 908-872-5723

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From: David, Jeannie C [mailto:Jeannie.David@fda.hhs.gov]
Sent: Friday, June 10, 2011 4:10 PM
To: Zezza, Charles [PRDUS]
Cc: Onaga, Linda
Subject: RE: PREZISTA Support

Dr. Zezza,

May we ask if Tibotec is still on track in providing the remainder of the responses to the May 25, 2011, CMC information request?

Also, we note that the samples provided this week did not contain the final syringe. When will the final syringe samples be sent?

Thank you,

Jeannie

Jeannie David, MS
Regulatory Health Project Manager
CDER/OPS/ONDQA
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 1475
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877
jeannie.david@fda.hhs.gov

From: Zezza, Charles [PRDUS] [mailto:CZezza@its.jnj.com]
Sent: Friday, June 10, 2011 3:56 PM
To: Onaga, Linda; David, Jeannie C
Subject: PREZISTA Support

Linda, Jeannie

I will be out of the office starting June 13th and will return on the afternoon of June 21st. I will be reading emails and checking voice mails at least once a day in the evenings. I will be several hours behind in terms of time zones so may not see emails until after your working hours are over.

If there are urgent issues that need immediate attention, please contact Rhonda Hatfield at 908 927-2598 (email rhatfiel@its.jnj.com).

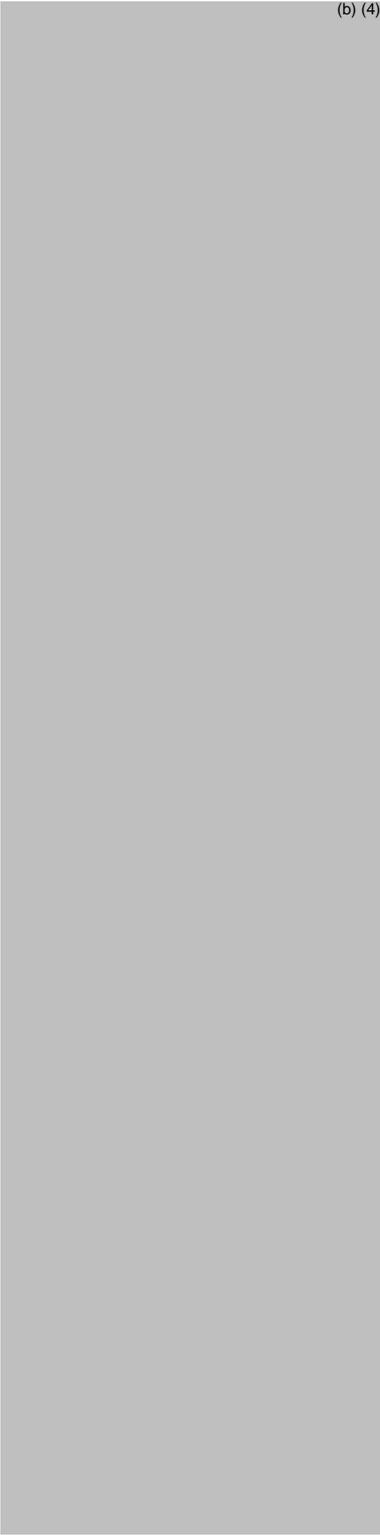
Best regards

Charles Zezza, Ph. D., MBA
Tibotec/J&JPRD
Office 908-707-3451 Cell 908-872-5723

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(b) (4)



(b) (4)



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/s/

JEANNIE C DAVID
07/15/2011



NDA 202-895

INFORMATION REQUEST

Tibotec, Inc.
Attention: Charles Zezza, Ph.D., M.B.A.
Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Dr. Zezza:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prezista (darunavir) Suspension, 100 mg/ml.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. In order to continue our evaluation of your NDA, we request your response by July 29, 2011.

1. Please revise the dissolution test acceptance criterion from $Q = \frac{(b)}{(4)}\%$ at 30 minutes to $Q = \frac{(b)}{(4)}\%$ at 30 minutes in order to ensure that a mean of 80% of the drug product is dissolved.
2. Please provide an explanation for the decreases in percent dissolved observed in the 6 week in-use stability samples (3.2.P.8.3, Table 2). Please also account for the wider range (min-max) of values observed in these samples compared to samples at release or on routine stability. To facilitate our review of this information, please submit the dissolution data collected from each sample.
3. Please describe the 'development method(s)' used for dissolution testing prior to establishment of the proposed regulatory method.
4. Provide the dissolution data supporting the selection of the dissolution medium and paddle speed for the proposed regulatory method.
5. The drug product specification includes a test for Resuspendability (Homogeneous after shaking, by Visual examination). Please refer to ICH Guidance "Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances."

3.3.2.2 Oral liquids, (j) *Redispersibility*: For oral suspensions that settle on storage (produce sediment), acceptance criteria for redispersibility may be

appropriate. Shaking may be an appropriate procedure. The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined.

Please provide information on the rate of settling of the drug product. Please identify the shaking procedure and time required to resuspend the drug product. Please comment on the implication for patient use and labeling directions.

If you have any questions, contact Jeannie David, Regulatory Project Manager, at (301) 796-4247, or jeannie.david@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
07/08/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: July 8, 2011

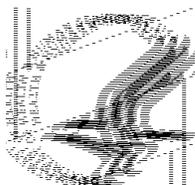
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: July 8, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202895

Please reference your submissions dated March 30, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

1. For the TMC114-C169 trial, please provide a table summarizing the total grams of fat, carbohydrates and proteins, and the total kcal and the kcal of fat, carbohydrates and proteins for the standardized breakfast that was administered to healthy subjects receiving either darunavir tablets or suspension under fed conditions.
2. For the TMC114-C169 trial, please clarify whether the administration of medications was standardized-for example, for all subjects, was darunavir/ritonavir administered 30 minutes after the start of the meal within 10 minutes?
3. For the TMC114-C228 trial, please clarify if the subjects were provided specific instructions on the type of meal that should be taken with darunavir/ritonavir or if a standard meal was administered to subjects during clinic visits when intensive or sparse PK blood samples were drawn. If yes, please provide the information specified in Question 1.

Please provide the Division with your response no later than Wednesday, July 22, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
07/08/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: June 29, 2011

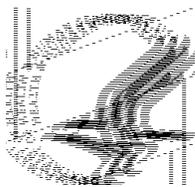
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 SN 8 and 14	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: June 29, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202895 SN 8 and 14

Please reference your submissions dated June 2 and 23, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) In the responses to the Clinical Pharmacology comments that were submitted on June 2, 2011 and June 23, 2011, it was indicated that the BA 819 and PBRL-RD-1041 method validations and the QCs, blanks and calibrations standards for the TMC114-C169 and TMC114-C228 trials were prepared in lithium heparin anticoagulated plasma.
 - A) For the TMC114-C169 plasma samples from individual subjects, please clarify whether blood samples were drawn in tubes with lithium heparin or sodium heparin as an anticoagulant.
 - B) For the TMC114-C228 plasma samples from individual subjects, please confirm that blood samples were drawn in tubes with sodium heparin as an anticoagulant.
 - C) Because of the differences in the anticoagulant used between QCs, blanks and calibrations standards (both for the method validation and for bioanalysis) and blood samples from subjects in the TMC114-C228 trial, we recommend that (b) (4)

conduct an additional validation experiment for darunavir and ritonavir to determine the impact of the differences in the anticoagulant used on the reported darunavir and ritonavir plasma concentrations. A similar experiment is also recommended for Janssen if a different anticoagulant was used for drawing blood samples in the TMC114-C169 trial.

- 2) For the darunavir/ritonavir method validated at (b) (4) (PBRL-RD-1041), please clarify whether the matrix effects experiment compares the recovery of the samples before and after protein precipitation.

Please provide the Division with your response no later than Wednesday, July 13, 2011.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
06/29/2011



NDA 202-895

INFORMATION REQUEST

Tibotec, Inc.
Attention: Charles Zezza, Ph.D., M.B.A.
Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Dr. Zezza:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prezista (darunavir) Suspension, 100 mg/ml.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. In order to continue our evaluation of your NDA, we request your response by July 9, 2011.

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.

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.

If you have any questions, contact Jeannie David, Regulatory Project Manager, at (301) 796-4247, or jeannie.david@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
06/27/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: June 17, 2011

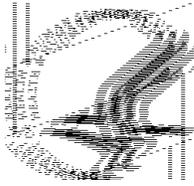
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 SN 1 Additional information request	

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: June 17, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202895 SN 8 Clarification to June 13, 2011 Comments

Please reference your submission dated June 2, 2011 and FDA comments dated June 13, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

Clinical Pharmacology :

- 1) b) Please provide information on the differences in the ritonavir boosting effects on darunavir exposure between a) the European and US marketed ritonavir solution, and b) the European and US marketed capsules **if there is a difference in the bioavailability between the European and US marketed ritonavir capsules or the European and US marketed ritonavir solution.**

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
06/17/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: June 13, 2011

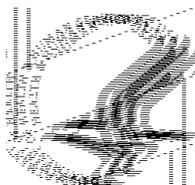
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDAs 21976 and 202895 Pediatric Exclusivity	

Total number of pages including cover: 3

Comments:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903**MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE**

NDA: 021976 and 202895

Drug: Prezista (daunavir) tablets and oral suspension

Date: June 13, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDAs 21976 and 202895 Pediatric Exclusivity

Pediatric Exclusivity has been granted for studies conducted on Preszita® (darunavir), effective June 7, 2011 under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Best Pharmaceuticals for Children Act (BPCA). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book. For additional information, please see the Guidance for Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080558.pdf>).

In accordance with section 505A(e)(1) of the Act, as amended by FDAAA (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made, on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Amendments Act of 2007, requires for one year after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted

Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

We are providing this above information via electronic facsimile for your convenience. Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
06/13/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: June 13, 2011

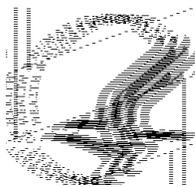
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 SN 1 Additional information request	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: June 13, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202-895 SN 8 Additional information request

Please reference your submission dated June 2, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

Clinical Pharmacology:

- 1) a) In the responses that were submitted on June 2, 2011, for question 20, please provide further information on the differences between a) the European and US marketed ritonavir solution, and b) the European and US marketed ritonavir capsules, including information on differences in human bioavailability, composition of the formulations, and dissolution profiles.

b) Please provide information on the differences in the ritonavir boosting effects on darunavir exposure between a) the European and US marketed ritonavir solution, and b) the European and US marketed capsules.
- 2) Please submit the bioanalytical study reports containing the ISR results that were generated from the following two trials: a) the telaprevir-darunavir/ritonavir trial at Janssen Research and b) the TMC114-C229 trial at (b) (4).

- 3) Please clarify whether the darunavir/ritonavir assay validated at (b) (4) is the same method that was validated at Janssen under BA819 or the same method that was validated at Janssen under BA502.
- 4) For the bioanalysis of TMC114-C169 plasma samples, please clarify whether the QCs, calibration and blank samples were prepared in lithium heparin or sodium heparin plasma. Please also specify whether the following darunavir and ritonavir method validations were validated in lithium heparin or sodium heparin: a) BA502 and b) BA 819.
- 5) In the responses that were submitted on June 2, 2011, for question 10, please clarify whether the scientific investigation determined possible causes for the failure of the darunavir LLOQ in run 11 for the TMC114-C228 trial.
- 6) To provide a comprehensive list of all the existing bioanalytical documents for darunavir/ritonavir, please provide a table with the appropriate cross references for the following: a) the BA502 method validation report and all the BA502 method validation amendments, b) the BA819 method validation report and all the BA819 method validation amendments, and c) the PBRL-RD-1041 method validation report and all the method validation amendments. If the materials have not been previously provided, please submit the materials.

Please provide a response to the Division no later than Friday, June 24, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
06/13/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: June 2, 2011

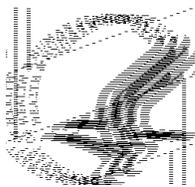
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 SN 1 Additional information request	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: June 2, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202-895 SN 1 Additional information request

Please reference your submission dated March 29, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

Clinical Pharmacology:

1) Please submit the following report (reference 30 for the TMC114-C228 trial report):

Treijtel N. A Phase II, open-label trial to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV in combination with low dose ritonavir (DRV/rtv) in treatment experienced HIV-1 infected children from 3 years to < 6 years of age. This trial will be referred to as ARIEL (noncompartmental analysis of the main study). Kinesis, Clinical Pharmacokinetic Report CD100041/TMC114-C228, December 2010.

Please provide a response to the Division no later than Friday, June 13, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
06/02/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: May 31, 2011

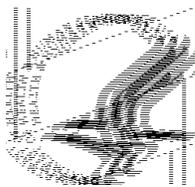
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 Revised Filing Communication	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: May 31, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Subject: NDA 202895 Revised Filing Communication

Please reference your submission dated March 29, 2011. We acknowledge a mistake on page 3 of the filing communication dated May 25, 2010.

Original Text on May 25, 2011:

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

Revised Text:

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

Please find attached the revised Filing Communication, with the updated information.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research



NDA 202895

FILING COMMUNICATION

Tibotec, Inc
Attention: Charles Zezza, Ph.D., M.B.A.
Director, Global Regulatory Affairs
920 Route US Highway 202S
PO Box 300
Raritan, NJ 08869

Dear Dr. Zezza:

Please refer to your New Drug Application (NDA) dated March 29, 2011 received March 30, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Prezista[®] (darunavir) oral suspension, 100 mg/mL.

We also refer to your submissions dated:

April 13, 2011
April 28, 2011
May 10, 2011.

April 19, 2011
May 3, 2011

April 26, 2011
May 9, 2011

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 30, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 9, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Please add the new dosage form and the route of administration for the new suspension formulation in the section immediately following the Highlights limitation sentence.
2. Recent Major Changes:
 - a. [REDACTED] (b) (4) must be removed because the one year time period has expired.
 - b. Please remove extra bullet under Warning and Precautions.
3. Dosage Forms and Strengths
 - a. Please place the dosage forms on two different lines and add bullets at the beginning of each:
 - 100 mg/mL oral suspension (3)
 - 75mg tablets, 150 mg tablets, 400 mg tablets and 600 mg tablets (3)
4. Contraindications
 - a. The second summarized statement in this section should reference the section (s) or subsection(s) of the Full Prescribing Information that contains detailed information.
5. Use in Specific Population:
 - a. Please remove [REDACTED] (b) (4) from the Highlights section and replace with “Pregnancy registry available. (8.1)”

FULL PRESCRIBING INFORMATION: CONTENTS*

6. Section 6 ADVERSE REACTIONS
 - a. Under 6.4, indent the second line of the text.
7. Section 13 NONCLINICAL TOXICOLOGY
 - a. Section 13.1 should be listed as “Carcinogenesis, mutagenesis, impairment of fertility”.

FULL PRESCRIBING INFORMATION

8. Section 17
 - a. The bracketed information directly under 17 Patient Counseling Information should be revised to *[See FDA-Approved Patient Labeling (Patient Information)]*
 - b. Section 17.1 General. Please create a new subsection heading. Avoid using words such as “General”, “Other”, or “Miscellaneous” for a subsection heading. Also, please update this section with the new subsection heading in the Full Prescribing information: Contents*.

PATIENT PACKAGE INSERT

9. Please add the following side effects statement **verbatim** to the PPI: **“Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-**

FDA-1088.” This must be used and cannot be modified to include applicant or manufacture’s phone number.

We request that you resubmit labeling that addresses these issues by June 10, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Antiviral Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Linda Onaga, Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
05/31/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: May 25, 2011

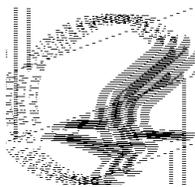
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 SN 1 Additional information request	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: May 25, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Peyton Myers, Ph.D., Pharmacology/Toxicology Reviewer
Hanan Ghantous, Ph.D., DABT Pharmacology/Toxicology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202-895 SN 1 Additional information request

Please reference your submission dated March 29, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

Pharmacology/Toxicology:

- 1) Please update the label in Section 8.1 to reflect the new Embryofetal Development data in rats which was submitted to fulfill the PMR titled "Perform a nonclinical reproductive toxicology study in a relevant species which achieves an adequate AUC exposure margin (compared to human serum exposure) in order to establish the safety profile of darunavir in utero. Submit your protocol for review prior to initiation of the reproductive toxicology study."

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
05/25/2011



NDA 202895

FILING COMMUNICATION

Tibotec, Inc
Attention: Charles Zezza, Ph.D., M.B.A.
Director, Global Regulatory Affairs
920 Route US Highway 202S
PO Box 300
Raritan, NJ 08869

Dear Dr. Zezza:

Please refer to your New Drug Application (NDA) dated March 29, 2011 received March 30, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Prezista[®] (darunavir) oral suspension, 100 mg/mL.

We also refer to your submissions dated:

April 13, 2011
April 28, 2011
May 10, 2011.

April 19, 2011
May 3, 2011

April 26, 2011
May 9, 2011

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 30, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 9, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Please add the new dosage form and the route of administration for the new suspension formulation in the section immediately following the Highlights limitation sentence.
2. Recent Major Changes:
 - a. [REDACTED] (b) (4) must be removed because the one year time period has expired.
 - b. Please remove extra bullet under Warning and Precautions.
3. Dosage Forms and Strengths
 - a. Please place the dosage forms on two different lines and add bullets at the beginning of each:
 - 100 mg/mL oral suspension (3)
 - 75mg tablets, 150 mg tablets, 400 mg tablets and 600 mg tablets (3)
4. Contraindications
 - a. The second summarized statement in this section should reference the section (s) or subsection(s) of the Full Prescribing Information that contains detailed information.
5. Use in Specific Population:
 - a. Please remove [REDACTED] (b) (4) from the Highlights section and replace with “Pregnancy registry available. (8.1)”

FULL PRESCRIBING INFORMATION: CONTENTS*

6. Section 6 ADVERSE REACTIONS
 - a. Under 6.4, indent the second line of the text.
7. Section 13 NONCLINICAL TOXICOLOGY
 - a. Section 13.1 should be listed as “Carcinogenesis, mutagenesis, impairment of fertility”.

FULL PRESCRIBING INFORMATION

8. Section 17
 - a. The bracketed information directly under 17 Patient Counseling Information should be revised to *[See FDA-Approved Patient Labeling (Patient Information)]*
 - b. Section 17.1 General. Please create a new subsection heading. Avoid using words such as “General”, “Other”, or “Miscellaneous” for a subsection heading. Also, please update this section with the new subsection heading in the Full Prescribing information: Contents*.

PATIENT PACKAGE INSERT

9. Please add the following side effects statement **verbatim** to the PPI: **“Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-**

FDA-1088.” This must be used and cannot be modified to include applicant or manufacture’s phone number.

We request that you resubmit labeling that addresses these issues by June 10, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Antiviral Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Linda Onaga, Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
05/25/2011
for D. Birnkrant



NDA 202-895

INFORMATION REQUEST

Tibotec, Inc.
Attention: Charles Zezza, Ph.D., M.B.A.
Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Dr. Zezza:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prezista (darunavir) Suspension, 100 mg/ml.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. In order to continue our evaluation of your NDA, we request your response by June 15, 2011.

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>".

We note 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>.

1. Clarify whether microbial limits testing will be performed as part of the release testing of every product batch.
2. 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.
3. 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.

4. 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.

In addition, we request the following:

5. Please provide a sample of the complete to-be-marketed container/closure system (bottle, cap, (b) (4)) with insert and dosing (b) (4). We request that you send the sample directly to Jeannie David, Regulatory Project Manager, at the address provided below. In addition, submit an amendment to NDA 202-895 to state that the sample was sent and when.

Jeannie David, MS
Regulatory Health Project Manager
CDER/OPS/ONDQA
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 1475
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877
jeannie.david@fda.hhs.gov

If you have any questions, contact Jeannie David, Regulatory Project Manager, at (301) 796-4247, or jeannie.david@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
05/25/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: May 17, 2011

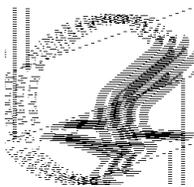
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 SN 1 Additional information request	

Total number of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: May 17, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202-895 SN 1 Additional information request

Please reference your submission dated March 29, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

Clinical Pharmacology:

- 1) Please clarify whether the temperature(s) that long term sample stability was evaluated at (-20°C) for both darunavir and ritonavir by Tibotec was the storage temperature(s) throughout the life cycle of the PK samples from the following two trials: TMC114-C169 and TMC114-C228 at the clinical trial sites, the bioanalytical laboratories and, if applicable, at any storage facilities for the samples.
- 2) Please provide the recertification dates and the relevant certificates of analysis, if applicable, for the darunavir and ritonavir reference standards and the darunavir and ritonavir internal standards that were used in generating the long term stability data in Amendment 5 for the BA502 method validation.

Please provide a response to the Division no later than Friday, June 3, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
05/17/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: May 12, 2011

To: Charles Zezza, PhD MBA

From: Linda C. Onaga, M.P.H.

Company: Tibotec

Title: Regulatory Project Manager

Fax number: 908-704-1501

Fax number: 301-796-9883

Phone number: 908-707-3451

Phone number: 301-796-0759

Subject: NDA 202895 SN 1 Additional information request

Total number of pages including cover: 5

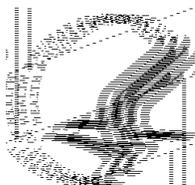
Comments:

Document to be mailed:

YES

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: May 12, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Kevin Krudys, PhD, Pharmacometrics Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202-895 SN 1 Additional information request

Please reference your submission dated March 29, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

Clinical Pharmacology:

A. Bioanalytical report for TMC114-C228 trial

1. Please clarify the following:
 - a. Are the darunavir reference standards with retest (expiry) dates of October 31, 2009 and October 31, 2010 the only reference standards that were used to analyze subject samples for the TMC114-C228 trial?
 - b. Were the darunavir stock solutions prepared prior to the retest dates of October 31, 2009 and October 31, 2010 for the darunavir reference standards and used within the 6 month stability period in preparing calibration curve standards and quality control samples?

2. In section 2.1, the reference for 1064 days of darunavir long-term stability data is the (b) (4) darunavir method validation report (PBRL-RD-1041). This report does not contain long-term stability data. Please clarify whether (b) (4) conducted separate long-term stability experiments or whether the long-term stability data generated by Tibotec is the correct reference.
3. Please clarify whether the QCs, calibration and blank samples were prepared in lithium heparin or sodium heparin plasma. Please also specify whether the (b) (4) darunavir and ritonavir method validation (PBRL-RD-1041) was validated in lithium heparin.
4. In runs (b) (4), please provide the criteria that used to determine that the contamination did not impact the reported plasma concentration results.
5. Please provide additional information for the following issues regarding the analytical runs:
 - a. Clarify why runs (b) (4) were analyzed for darunavir concentrations only.
 - b. Was the reason for the failure of the QCs in run (b) (4) further investigated?
 - c. Was the reason for the unacceptable carryover in run (b) (4) further investigated?
6. Please clarify why a “medium high” QC sample of 1500 ng/mL for darunavir and ritonavir was added to sample runs starting with run (b) (4).
7. In Tables 8 and 9, please clarify whether the reanalysis result is the result of two separate concentration results that are not displayed.
8. Please clarify whether there were any samples where both the undiluted and diluted samples resulted in plasma concentrations that were within the calibration curve range. If yes, please clarify how the reported concentration was determined.
9. In Tables 2 and 3, was the reason for the failure of the low QC (15 ng/mL) to meet acceptance criteria in multiple runs and the medium QC (250 ng/mL) in run (b) (4) further investigated, especially for the low QC in run (b) (4) with an accuracy of (b) (4) %? (4)
10. Please specify whether the cause of the failure of the LLOQ in run (b) (4) was further investigated and clarify whether there were any samples between 5 and 10 ng/mL that required reanalysis.

B. Bioanalytical report for TMC114-C169 trial

11. Please clarify the rationale for using different darunavir and ritonavir medium and high QC concentrations (240 ng/mL and 7680 ng/mL, respectively) than were evaluated in the BA819 method validation (258 ng/mL and 7580 ng/mL, respectively).
12. Please clarify whether the samples in Table 5-5 were reanalyzed once, in duplicate, or triplicate.

13. Please provide further information on the analytical error that caused run (b) (4) to be rejected and whether the analytical error required further investigation.

14. Was the reason for the failure of the darunavir QCs in run (b) (4) further investigated?

C. Bioanalytical reports for TMC114-C169 and TMC114-C228 trials

15. Please clarify whether incurred sample reanalysis (ISR) was conducted for either the TMC114-C228 or the TMC114-C169 plasma samples. We recommend that ISR be conducted for darunavir and ritonavir in both trials if it has not been conducted.

D. PBRL-RD-1041 method validation report

16. In section 2.5.7, the method validation report references 1245 days at 4°C of ritonavir stock solution stability data in assay method report PBRL-RD-682. Please clarify whether additional stock solution stability data was generated for either darunavir or ritonavir for another method validation other than for BA136.

17. Please submit the method validation report or reports, including BA136, with the current darunavir and ritonavir stock solution stability data.

18. In Tables 16 and 17, please clarify whether the cause of the quantifiable darunavir and ritonavir concentrations in the blank samples was investigated.

E. Comments for the TMC114-C169 and TMC114-C228 trials

19. Please confirm that the 300 mg darunavir tablet administered in the TMC114-C169 trial was the 300 mg tablet formulation that was previously commercially marketed in the US.

20. Please confirm that the 100 mg ritonavir capsule administered in the TMC114-C169 trial and the 80 mg/mL ritonavir solution administered in the TMC114-C228 trial are the commercially marketed formulations in the US.

21. In the TMC114-C169 trial, the darunavir suspension was administered with ritonavir capsules. Please provide information from the published literature or previous darunavir trials evaluating the anticipated differences in darunavir exposure when darunavir suspension is coadministered with ritonavir solution compared to darunavir suspension coadministered with ritonavir capsules.

Please provide a response to the Division no later than Friday, June 3, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
05/13/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: May 3, 2011

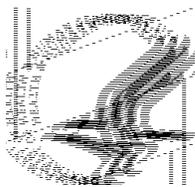
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202895 SN 1 Additional information request	

Total number of pages including cover: 3

Comments:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202895

Drug: Prezista (daunavir) oral suspension

Date: May 3, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Kevin Krudys, PhD, Pharmacometrics Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader
Regina Alivisatos, MD, Clinical Reviewer
Yodit Belew, MD, Clinical Team Leader

Subject: NDA 202-895 SN 1 Additional information request

Please reference your submission dated March 29, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

Clinical Pharmacology:

- 1) The TMC114-C228 bioanalytical report states that 53 samples remain to be analyzed. Please provide additional information on the 53 samples. Specifically, please clarify whether there are additional pediatric subjects whose PK samples remain to be analyzed for twice-daily darunavir dose administration, miscellaneous samples from some subjects that need to be analyzed, or if the samples are related to the once daily subtrial.
- 2) Please clarify whether the population PK analysis for TMC114-C228 trial evaluating twice-daily darunavir dose administration needs to be updated to include the plasma concentration data from the 53 samples.

- 3) Please clarify whether the TMC114-C228 bioanalytical report includes plasma concentration data for samples analyzed in the once daily subtrial or if these samples will be analyzed separately.

Pharmacometrics:

Please submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:

- 4) Model codes or control streams and output listings should be provided for the Week 2 interim analysis (Appendix C of the Population PK Report) and the Week 24 analysis (Appendix D of the Population PK Report). These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- 5) Datasets used for the Week 2 interim analysis (Appendix C of the Population PK Report) and the Week 24 analysis (Appendix D of the Population PK Report) should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Please provide a response to the Division no later than May 10, 2011.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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LINDA C ONAGA
05/03/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: April 14, 2011

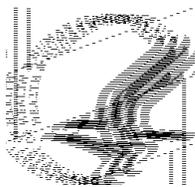
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202-895 SN 1 Additional information request	

Total number of pages including cover: 2

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202-895

Drug: Prezista (daunavir) oral suspension

Date: April 14, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, PharmD., Clinical Pharmacology Team Leader

Subject: NDA 202-895 SN 1 Additional information request

Please reference your submission dated March 29, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) Please provide the following information:
 - a) Bioanalytical laboratory that analyzed plasma samples for the TMC114-C169 trial:
name, address, phone, fax, contact person
 - b) Bioanalytical laboratory that analyzed plasma samples for the TMC114-C228 trial:
name, address, phone, fax, contact person

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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LINDA C ONAGA
04/14/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: April 6, 2011

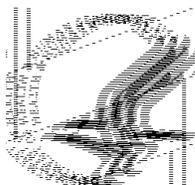
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-0759
Subject: NDA 202-895 SN 1 Additional information request	

Total number of pages including cover: 2

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202-895

Drug: Prezista (daunavir) oral suspension

Date: April 6, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Vikram Arya, Ph.D., Acting Clinical Pharmacology Team Leader
Regina Alivisatos, M.D., Clinical Reviewer
Yodit Belew, MD, Clinical Reviewer Team Leader

Subject: NDA 202-895 SN 1 Additional information request

Please reference your submission dated March 29, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) Please submit the bioanalytical reports for the TMC114-C169 and TMC114-C228 trials (R319064/048 and TMC114/059, respectively).

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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LINDA C ONAGA
04/06/2011



NDA 202-895

NDA ACKNOWLEDGMENT

Tibotec, Inc
Attention: Charles Zezza, Ph.D., M.B.A.
Director, Global Regulatory Affairs
920 Route US Highway 202S
PO Box 300
Raritan, NJ 08869

Dear Dr. Zezza:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Prezista® (darunavir) suspension, 100 mg/mL

Date of Application: March 29, 2011

Date of Receipt: March 30, 2011

Our Reference Number: NDA 202-895

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call Linda Onaga, Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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LINDA C ONAGA
04/04/2011