

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202895Orig1s000

OTHER REVIEW(S)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 021976 202895 BLA # N/A	NDA Supplement # S-020 S-000 BLA STN # N/A	If NDA, Efficacy Supplement Type: SE-05
Proprietary Name: Prezista Established/Proper Name: darunavir Dosage Form: Tablets and Oral Suspension		Applicant: Tibotec, Inc Agent for Applicant (if applicable): N/A
RPM: Linda C. Onaga, MPH		Division: DAVP
<p><u>NDA</u>s:</p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.</p> <p><input type="checkbox"/> This application relies on a final OTC monograph.</p> <p><input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 30, 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): Type 3 (New Formulation)</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input checked="" type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input checked="" type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other DAVP listserv

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	December 16, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) December 16, 2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	December 15, 2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	March 30, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	December 15, 2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	September 9, 2011 (IFU) March 30, 2011 (USPI and USPPPI)
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	N/A
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM June 23, 2011 December 16, 2011 <input type="checkbox"/> DMEPA December 13, 2011 August 31, 2011 <input type="checkbox"/> DRISK December 14, 2011 September 28, 2011 September 6, 2011 <input checked="" type="checkbox"/> DDMAC September 2, 2011 July 26, 2011 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	August 5, 2011
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>August 17, 2011</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 14, 2011 September 16, 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 1
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	December 13, 2011 September 6, 2011 May 9, 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical Review - September 6, 2011 Page 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A <input checked="" type="checkbox"/> None N/A
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 25, 2011 April 26, 2011
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 27, 2011
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 8, 2011 September 6, 2011 April 29, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None August 5, 2011
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 31, 2011 May 26, 2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Product Quality September 29, 2011 Product Quality September 6, 2011 Product Quality May 2, 2011 Biopharmaceutics September 1, 2011
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed August 10, 2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Product Quality Review : September 6, 2011
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: May 20, 2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

LINDA C ONAGA
12/16/2011

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 202895
NDA 21976/S-20

Name of Drug: Prezista[®] oral suspension, 100mg/mL
Prezista[®] tablets, 75 mg, 150 mg, 400 mg, and 600 mg

Applicant: Tibotec, Inc

Labeling Reviewed

Submission Date: December 15, 2011

Receipt Date: December 15, 2011

Submission Date of SPL: March 30, 2011 and June 28, 2011

Type of Labeling Reviewed: WORD

Material Reviewed: Last approved labeling for NDA 21976 (S-18) approved October 19, 2011 and Proposed Labeling and Instructions for use for NDA 202895 and NDA 21976/S-20 amended December 15, 2011

Background and Summary Description:

In response to FDA's Written Request and PREA PMR 389-1, Tibotec submitted, an original NDA for Prezista oral suspension formulation. Because the oral solution formulation will share labeling with the tablet formulation, Tibotec submitted an efficacy supplement for the Prezista tablet formulation. The NDA data will support the use of Prezista in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric populations from 3 to less than 6 years of age (10 kg to less than ^(b)₍₄₎ kg), 6 to less than 18 years of age (20 kg to less than 40 kg), and treatment experienced and treatment naïve HIV-1 infected adult populations. The original NDA provides pharmacokinetic, safety, tolerability and virologic response data that supports weight-based dosing recommendations of Prezista in combination with ritonavir for treatment experienced HIV-1 pediatric patients 3 to < 6 years of age.

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/s/

LINDA C ONAGA
12/16/2011

KAREN D WINESTOCK
12/16/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 14, 2011

To: Debra Birnkrant, MD, Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

Subject: DMPP Concurrence with submitted Instructions for Use

Drug Name (established name): PREZISTA (darunavir)

Dosage Form and Route: Oral Suspension

Application Type/Number: NDA 202-895
NDA 21-796/S-020

Applicant: Tibotec, Inc.

OSE RCM #: 2011-1372

1 INTRODUCTION

On March 30, 2011 Tibotec, Inc. submitted original NDA 202-895 for PREZISTA (darunavir) Oral Suspension which provides pharmacokinetic, safety, tolerability and virologic response data that supports weight-based dosing recommendations of PREZISTA in combination with ritonavir for treatment-experienced HIV-1 infected pediatric patients ages 3 to < 6 years. Labeling in the submission included expanded dosing recommendations for the age group 3 to < 6 years. DMPP completed a review of the Patient Package Insert on September 6, 2011, as requested by DAVP. On August 16, 2011 the Division of Antiviral Products held a teleconference with Tibotec, Inc. and requested that the Applicant submit Instructions for Use for the product.

On September 28, 2011, DMPP completed a review of the proposed PREZISTA (darunavir) Oral Suspension Instructions for Use (IFU) submitted on September 14, 2011. On December 12, 2011, Tibotec, Inc. submitted proposed revisions to the IFU for the Agency's review and approval.

2 MATERIAL REVIEWED

- Draft PREZISTA (darunavir) Oral Suspension Instructions for Use (IFU) submitted on December 12, 2011.

3 CONCLUSIONS

The Applicant's proposed IFU revisions are acceptable with the following comments:

- In Figure A, the Applicant should change (b) (4) to "use".
- In Figure (b) (4) the Applicant should use a lowercase 'b' in: "Closing the bottle".

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

BARBARA A FULLER
12/14/2011

LASHAWN M GRIFFITHS
12/14/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memorandum

Date: December 13, 2011

Reviewer: Loretta Holmes, BSN, PharmD
Division of Medication Error Prevention and Analysis
(DMEPA)

Team Leader Lubna Merchant, MS, PharmD
Division of Medication Error Prevention and Analysis
(DMEPA)

Division Director Carol A. Holquist, RPh
Division of Medication Error Prevention and Analysis
(DMEPA)

Drug Name and Strength: Prezista (Darunavir) Oral Suspension
100 mg per mL

Application Type/Number: NDA 202895

Applicant: Tibotec, Inc.

OSE RCM #: 2011-1370

1 INTRODUCTION

This memorandum responds to a request from the Division of Antiviral Products (DAVP) for DMEPA's evaluation of revised labels and labeling for Prezista oral suspension.

2 BACKGROUND

The Applicant submitted revised carton labeling and a revised syringe graphic on November 9, 2011 in response to recommendations from DMEPA that were forwarded to the Applicant on October 6, 2011 in an Information Request Letter. Additionally, the Applicant made changes to the container label (the location of the lot number and expiry was changed) that were not requested by DMEPA and submitted the revised container label containing those changes on November 30, 2011. DMEPA evaluated these labels and labeling (see Appendices A through C).

3 CONCLUSIONS AND RECOMMENDATIONS

The Applicant has implemented our recommendations for the carton labeling and syringe graphic and we find the revised carton labeling and syringe graphic submitted on November 9, 2011 acceptable. Additionally, we find the revised container label submitted on November 30, 2011 acceptable.

If you have further questions or need clarifications, please contact Brantley Dorch, OSE Project Manager, at 301-796-0150.

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/s/

LORETTA HOLMES
12/13/2011

LUBNA A MERCHANT
12/13/2011

CAROL A HOLQUIST
12/13/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

PATIENT LABELING REVIEW

Date: September 28, 2011

To: Debra Birnkrant, MD, Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Risk Management

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Instructions for Use)

Drug Name (established name): PREZISTA (darunavir)

Dosage Form and Route: Oral Suspension

Application Type/Number: NDA 202-895
NDA 21-976/S-20

Applicant: Tibotec, Inc.

OSE RCM #: 2011-1372

1 INTRODUCTION

This review is written in response to a request by the Division of Antiviral Products (DAVP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Instructions for Use (IFU) for PREZISTA (darunavir) Oral Suspension.

On March 30, 2011 Tibotec, Inc. submitted original NDA 202-895 for PREZISTA (darunavir) Oral Suspension which provides pharmacokinetic, safety, tolerability and virologic response data that supports weight-based dosing recommendations of PREZISTA in combination with ritonavir for treatment-experienced HIV-1 infected pediatric patients ages 3 to < 6 years. Labeling in the submission included expanded dosing recommendations for the age group 3 to < 6 years. DRISK completed a review of the Patient Package Insert on September 6, 2011, as requested by DAVP. On August 16, 2011 the Division of Antiviral Products held a teleconference with Tibotec, Inc. and requested that the Applicant submit Instructions for Use for the product..

2 MATERIAL REVIEWED

- Draft PREZISTA (darunavir) Oral Suspension and Tablet Prescribing Information (PI) received September 14, 2011 and sent to DRISK on September 20, 2011.
- Draft PREZISTA (darunavir) Oral Suspension Instructions for Use (IFU) received September 14, 2011 and sent to DRISK on September 20, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Verdana font, size 11.

In our review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DRISK and DMEPA comments.

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated (tracked and clean) versions of the IFU are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

STEVE L MORIN
09/28/2011

LASHAWN M GRIFFITHS
09/28/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

PATIENT LABELING REVIEW

Date: September 2, 2011

To: Debra Birnkrant MD, Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): PREZISTA (darunavir)

Dosage Form and Route: Oral Suspension and Tablets

Application Type/Number: NDA 21-976
NDA 202-895

Supplement number: S-018, S-020

Applicant: Tibotec, Inc.

OSE RCM #: 2011-245
2011-1372

1 INTRODUCTION

This review is written in response to a request by the Division of Antiviral Products (DAVP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for PREZISTA (darunavir) Oral Solution and Tablets.

On December 13, 2010, Tibotec, Inc received approval for New Drug Application (NDA) PREZISTA (darunavir) Tablets Prior Approval (PAS) supplement 017 for the treatment of Human Immunodeficiency Virus (HIV). The PAS allowed for a new dosing schedule to be included in the Prescribing Information. The Applicant submitted Prior Approval Supplement Labeling (sNDA21-976/S-018) on December 22, 2010 which provided proposed labeling to include the new labeling information as approved on Dec 13, 2010. The revisions to the Package Information (PI) did not require corresponding revisions to the Patient Package Insert (PPI).

On March 30, 2011 Tibotec, Inc. submitted original NDA 202-895 and NDA21-976/S-020 for PREZISTA (darunivar) Oral Solution and Tablets. Tibotec also has included study reports for pediatric use and is requesting pediatric exclusivity.

2 MATERIAL REVIEWED

- Draft Prezista (darunavir) Oral Solution and Tablet Patient Package Insert (PPI) received on March 30, 2011 and revised by the Review division throughout the current review cycle and sent to DRISK on August 22, 2011.
- Draft Prezista (darunavir) Oral Solution and Tablet Prescribing Information (PI) received March 30, 2011 and revised by the Review Division throughout the current review cycle and sent to DRISK on August 22, 2011.
- Approved Viramune (nevirapine) tablets and oral solution comparator labeling dated March 25, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated (tracked and clean) versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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STEVE L MORIN
09/02/2011

LASHAWN M GRIFFITHS
09/06/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 2, 2011

To: Linda Onaga, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Jessica Fox, PharmD, Regulatory Review Officer
Sheila Ryan, PharmD, Group Leader
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 202895 – Prezista (darunavir) oral suspension

As requested in DAVP's consult dated April 28, 2011, DDMAC has reviewed the Prezista prescribing information (PI), medication guide (med guide), and carton and container labeling, which have been updated to expand the indication to pediatric patients 3 years of age and older, and to include a new oral suspension dosage form.

Comments on the proposed med guide were sent under separate cover on July 26, 2011.

DDMAC's comments are provided directly below in the proposed substantially complete version of the PI provided by the DAVP eRoom on August 24, 2011. We have no comments at this time on the proposed carton and container labeling.

If you have any questions, please contact Jessica Fox at 6-5329 or at Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
09/02/2011



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

ELECTRONIC MAIL TRANSMITTAL SHEET

DATE: September 1, 2011

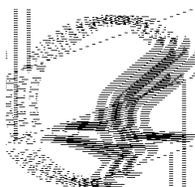
To: Charles Zezza, PhD MBA	From: Linda C. Onaga, M.P.H.
Company: Tibotec, Inc.	Title: Regulatory Project Manager
Fax number: 908-704-1501	Fax number: 301-796-9883
Phone number: 908-707-3451	Phone number: 301-796-3979
Subject: NDA 202895-Labeling Comments	

Total number of pages including cover: 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 1, 2011

To: Charles Zezza, PhD, MBA

Sponsor: Tibotec, Inc.

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

Concur: Wendy Carter, D.O., Acting Team Leader
Regina Alivisatos, M.D., Clinical Reviewer

Subject: NDA 202895-Labeling Comments

Please reference your submissions dated March 30, 2001. The following Division of Medication Error Prevention and Risk Management (DMEPA) comments is being conveyed on behalf of the review team for your application.

General Comment:

1. The statement of strength is presented as: "100 mg/mL". The slash mark appears on the Institute for Safe Medication Practices (ISMP) list of error-prone abbreviations, symbols and dose designations because it has been confused as the number "1". Therefore, we request you revise the statement of strength to read: "100 mg per mL".

Container Label:

2. Important statements concerning handling of the product are not prominent on the container label. Revise the following two statements so they appear in a bold font: "Do not refrigerate or freeze" and "Shake well before each usage" Additionally, relocate these statements to the principal display panel. To accommodate for this, relocate the statement "Each mL of the oral suspension..." from the principal display panel to the side panel.

Carton Labeling:

3. Important statements concerning handling of the product are not prominent on the carton labeling. Revise the following two statements so they appear in a bold font: “Do not refrigerate or freeze” and “Shake well before each usage”.
4. The principal display panel appears crowded. The statements “Avoid exposure to excessive heat” and “Store in the original container” are duplicative. Delete them from the principal display panel and keep them on the back panel. Additionally, delete the “Manufactured by...” and “Manufactured for...” statements from the principal display panel since they are already on the back panel.

Please provide the Division with your response no later than *Friday, September 9, 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.

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/

LINDA C ONAGA
09/01/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: August 30, 2011

Reviewer: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis
(DMEPA)

Team Leader Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis
(DMEPA)

Division Director Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
(DMEPA)

Drug Name: Prezista (Darunavir) Oral Suspension
100 mg per mL

Application Type/Number: NDA 202895

Applicant: Tibotec, Inc.

OSE RCM #: 2011-1370

***** This document contains proprietary and confidential information that should not be released to the public.*****

1 INTRODUCTION

This review evaluates the container label, carton and insert labeling submitted on March 29, 2011 for Prezista (Darunavir) Oral Suspension in response to a request from the Division of Antiviral Products (DAVP).

The NDA (021976) for Prezista tablets was approved on June 23, 2006. This new NDA (202895) provides for the use of Prezista in combination with ritonavir for treatment-experienced HIV-1 infected pediatric patients ages 3 to less than 6 years of age. This application also provides for a new oral dosage form (suspension).

1.1 PRODUCT INFORMATION

Prezista is a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV-1 infection in adult patients. Prezista is also indicated for the treatment of HIV-1 infection in pediatric patients 3 years of age and older. Prezista must be co-administered with ritonavir and with other antiretroviral agents. See Appendix A for the proposed dosing. Prezista oral suspension will be packaged in 200 mL amber bottles and supplied with a dosing (b) (4). The recommended storage temperature is 25°C; with excursions permitted to 15°C-30°C (59°F-86°F).

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following (see Appendices C through E):

- Container Labels submitted on March 29, 2011
- Carton Labeling submitted on March 29, 2011
- Insert Labeling submitted on March 29, 2011
- Container closure system (bottle, insert, cap) submitted on June 9, 2011
- Oral dosing (b) (4) submitted on August 12, 2011.

Additionally, since Prezista is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Prezista. The AERS search conducted on August 18, 2011 used the following search terms: active ingredient “darunavir”, trade name “Prezista%”, and verbatim terms “darun%” and “Prez%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. The time frame of the search was limited to April 16, 2010 through August 18, 2011. This covers the time period since our last search for medication errors involving Prezista in OSE Review 2011-831/2009-9, dated October 28, 2010.

Furthermore, since the (b) (4) proposed for use with Prezista oral suspension is similar to the (b) (4) used for Risperdal oral solution, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

involving use of the (b) (4) supplied with Risperdal Oral Solution. The AERS search conducted on July 26, 2011 used the following search terms: active ingredient “Risperidone%”, trade name “Risperdal%”, and verbatim term “Risp%”. The reaction terms used were the MedDRA Preferred Terms (PT): Medication Error, Drug Administration Error, Incorrect Dose Administered, Incorrect Dose Administered by Device, Wrong Technique in Drug Usage Process, Drug Label Confusion, Product Label Confusion, Accidental Overdose, Overdose, Underdose, Drug Prescribing Error, and Syringe Issue. No time limitation was set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels and labeling or dosing (b) (4), the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error or were not associated with the labels and labeling or the (b) (4).

3 EVALUATION OF FDA ADVERSE EVENTS REPORTING SYSTEM (AERS) CASES

Our search of the AERS database for medication errors involving Prezista tablets identified 18 medication error cases. Our search of the AERS database for medication errors involving the Risperidal oral (b) (4) identified 537 cases. See Appendix B for the ISR numbers of the reports identified in these two searches. Following exclusions we evaluated a total of four cases relevant to this review.

3.1 PREZISTA AERS SEARCH RESULTS (N=1)

We evaluated one report of dispensing the wrong strength.

- The case describes two different instances where Prezista 400 mg tablets were dispensed instead of the 600 mg strength. The reporter attributed the errors to poor color coding. The errors reached the patients. The outcome was not provided. (ISR# 7237840)

Our review of the Prezista container labels² noted the statement of strength on the 400 mg and 600 mg labels is in a green color block and orange color block, respectively, which appears to differentiate them. We compared the color block used to highlight the strength of Prezista oral suspension (rose) to those used on all four currently marketed strengths on Prezista tablets [75 mg (blue-green), 150 mg (brown), 400 mg (green), and 600 mg (orange)] and noted it is differentiated from those colors which may help to mitigate product strength selection errors.

² Labels obtained from DailyMed at: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=48576>. Accessed on August 16, 2011.

3.2 RISPERIDAL/RISPERIDONE AERS SEARCH RESULTS (N=3)

Three cases describe wrong dose errors related to the dosing device.

- A 6-year old boy was prescribed Risperdal 0.5 mg orally twice daily. The reporter stated the syringe is misleading in that the markings are on the plunger rather than the syringe casing and as a result, they are in opposite order from standard syringe markings. The father noted 0.5 mg on end of the syringe and assumed the full syringe to be 0.5 mg. The child was administered a full syringe of medicine (3 mg). The family sought medical attention. The child became symptomatic but responded to treatment. (ISR# 4744245, received August 2005)
- A mother mistakenly administered a tenfold dose of risperidone because she had problems with the handling of the (b) (4). A dose of 0.25 mL (0.25 mg) was prescribed for the child. Due to problems with handling the (b) (4), the mother administered 2.5 mL to 3 mL. The child became symptomatic, was hospitalized and later recovered. The reporter did not describe the problems the mother had with handling the (b) (4). (ISR# 5993454, received December 2008)
- A 10-year old was prescribed 0.25 mL (0.25 mg) of Risperidal twice daily. The mother had difficulty drawing up the correct dose because she pulled up air bubbles into the syringe. The child received an amount equated to 2 to 3 drops of medication. Patient's condition worsened. The child was switched from the oral solution to tablets and her condition improved. (ISR# 6368049, received September 2009)

One of the aforementioned cases stated the syringe markings are “in opposite order from standard syringe markings”, thus, we anticipate there could be confusion with the use of the Prezista dosing (b) (4) which is marked in a similar manner. We also note that one of the cases stated the markings are on the (b) (4) rather than the “syringe casing” which was also found to be confusing. Additionally, Prezista is described as a white to off-white opaque suspension and it is supplied in an amber bottle. Since the suspension is opaque and it is supplied in an amber bottle, there may be impaired visibility of the suspension as it is being pulled up into the dosing (b) (4) (about 80% of the length of the dosing (b) (4) is positioned inside the bottle when measuring a dose) that may lead to dosing errors. When using a “standard” oral dosing syringe, the syringe is outside the bottle as the medication is being pulled up which may help patients to see the medication as it is being pulled up and identify air bubbles or other problems and make any corrections needed to help ensure the correct dose is measured.

4 DISCUSSION OF DEFICIENCIES IDENTIFIED

Our review of the labels, labeling, and product packaging identified the deficiencies discussed below.

(b) (4)

4.2 CONTAINER LABELS AND CARTON LABELING

- The statement of strength contains a slash mark which is on the Institute for Safe Medication Practices (ISMP) list of error-prone abbreviations, symbols and dose designations.
- Important statements concerning handling of the product are not prominent.

4.3 INSERT LABELING

The insert labeling is currently a working document requiring frequent revisions. We reserve review of and recommendations for the insert labeling for the labeling meetings scheduled with the Division of Antiviral Products (DAVP). Our recommendations will be made to the working insert labeling that is available in the DAVP eRoom.

5 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label, labeling and design introduce vulnerability that can lead to medication errors. We find the proposed (b) (4) unacceptable because patients and caregivers may find it confusing and may not be able to use it safely because it is numbered in a direction that is opposite to standard oral syringes. DMEPA communicated this to the Applicant in a teleconference held on August 26, 2011. The Applicant agreed to provide a standard oral syringe with the product and a plug for the bottle opening that will accommodate the oral syringe during dose measurement. We recommend the following recommendations be implemented prior to approval:

A. Product Design

We have received postmarketing dosing errors with a product that uses a (b) (4) similar to that proposed for Prezista oral suspension. Thus, we do not recommend the use of the proposed dosing (b) (4) with this product. We recommend the use of a standard oral syringe. Additionally, we recommend a plug for the bottle neck opening to accommodate the oral syringe tip during dose measurement.

B. General Comment

The statement of strength is presented as: “100 mg/mL”. The slash mark appears on the Institute for Safe Medication Practices (ISMP) list of error-prone abbreviations, symbols and dose designations because it has been confused as the number “1”. Therefore, we request you revise the statement of strength to read: “100 mg per mL”.

C. Container Label

Important statements concerning handling of the product are not prominent on the container label. Revise the following two statements so they appear in a bold font: “Do not refrigerate or freeze” and “Shake well before each usage” Additionally, relocate these statements to the principal display panel. To accommodate for this, relocate the statement “Each mL of the oral suspension...” from the principal display panel to the side panel.

D. Carton Labeling

1. Important statements concerning handling of the product are not prominent on the carton labeling. Revise the following two statements so they appear in a bold font: “Do not refrigerate or freeze” and “Shake well before each usage”.
2. The principal display panel appears crowded. The statements “Avoid exposure to excessive heat” and “Store in the original container” are duplicative. Delete them from the principal display panel and keep them on the back panel. Additionally, delete the “Manufactured by...” and “Manufactured for...” statements from the principal display panel since they are already on the back panel.

E. Insert Labeling

Provide clear instructions for use of the oral dosing syringe that will be supplied with the product.

If you have further questions or need clarifications, please contact Brantley Dorch, OSE Project Manager, at 301-796-0150.

APPENDICES

Appendix A: Prezista Dosage

- Treatment-naïve adult patients and treatment-experienced adult patients with no darunavir resistance associated substitutions: 800 mg (two 400 mg tablets) taken with ritonavir 100 mg once daily and with food.
- Treatment-experienced adult patients with at least one darunavir resistance associated substitution: 600 mg (one 600 mg tablet) taken with ritonavir 100 mg twice daily and with food.
- Pediatric patients (3 to less than 18 years of age and weighing at least 10 kg): dosage of PREZISTA and ritonavir is based on body weight and should not exceed the treatment-experienced adult dose. Do not use once daily dosing in pediatric patients. PREZISTA should be taken with ritonavir twice daily and with food.

Dosing recommendations for pediatric patients weighing at least 10 kg but less than 15 kg

The weight-based dose in pediatric patients weighing less than 15 kg is PREZISTA ^(b)₍₄₎ mg/kg with ritonavir 3 mg/kg which can be dosed using the following table:

Table 1: Recommended Dose for Pediatric Patients with PREZISTA Oral Suspension and Ritonavir Oral Solution for Pediatric Patients Weighing 10 kg to Less Than 15 kg*	
Body weight (kg)	Dose (twice daily)
Greater than or equal to 10 kg to less than 11 kg	PREZISTA ^(b) ₍₄₎ with ritonavir 32 mg (0.4 mL)
Greater than or equal to 11 kg to less than 12 kg	PREZISTA with ritonavir 32 mg (0.4 mL)
Greater than or equal to 12 kg to less than 13 kg	PREZISTA with ritonavir 40 mg (0.5 mL)
Greater than or equal to 13 kg to less than 14 kg	PREZISTA with ritonavir 40 mg (0.5 mL)
Greater than or equal to 14 kg to less than 15 kg	PREZISTA with ritonavir 48 mg (0.6 mL)
*ritonavir oral solution: 80 mg/mL	

Dosing recommendations for pediatric patients weighing at least 15 kg

Pediatric patients who weigh at least 15 kg and are able to swallow tablets can be dosed using the following table:

Table 2: Recommended Dose for Pediatric Patients with PREZISTA Tablets and Ritonavir Oral Solution or Tablets/Capsules for Pediatric Patients Weighing At Least 15 kg	
Body Weight (kg)	Dose (twice daily)
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 375 mg with ritonavir* 50 mg (0.6 mL)
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 450 mg with ritonavir* 60 mg (0.75 mL)
Greater than or equal to 40 kg	PREZISTA 600 mg with ritonavir [†] 100 mg
*with ritonavir oral solution: 80 mg/mL	
† with ritonavir capsules or tablets: 100 mg	

Pediatric patients who weigh at least 15 kg but are unable to swallow tablets can be dosed using the following table:

Table 3: Recommended Dose for Pediatric Patients with PREZISTA Oral Suspension and Ritonavir Oral Solution* for Pediatric Patients Weighing At Least 15 kg	
Body Weight (kg)	Dose (twice daily)
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 375 mg (3.8 mL) with ritonavir 50 mg (0.6 mL)
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 450 mg (4.6 mL) with ritonavir 60 mg (0.75 mL)
Greater than or equal to 40 kg	PREZISTA 600 mg (6.0 mL) with ritonavir 100 mg (1.25 mL)
*with ritonavir oral solution: 80 mg/mL	

Appendix B: AERS Cases ISR Numbers

Prezista AERS Cases

ISR Numbers					
6715806	6789795	7125380	7322810	7492176	7609956
6747456	6933644	7237840	7358450	7511353	7638437
6768069	7109030	7289511	7375676	7588723	7673341

Risperidal/Risperidone AERS Cases

ISR Numbers					
1483102	3707248	4792004	5793511	6571702	7421469
1483815	3710591	4793405	5797839	6571980	7422746
1484874	3729363	4800169	5807380	6575735	7425811
1492451	3753244	4803380	5809612	6584150	7456771
1498989	3764205	4804728	5814909	6590897	7463320
1498994	3764263	4819431	5815197	6595480	7468932
1499004	3792810	4820611	5818437	6598650	7472230
1499009	3801768	4823944	5819684	6607793	7475309
1499012	3820033	4825343	5847745	6608631	7481743
1525923	3825926	4840701	5848974	6613486	7487827
1526742	3844404	4852389	5849196	6613488	7492987
1529926	3844582	4867898	5850538	6616136	7495614
1536474	3867394	4883122	5862050	6639552	7516950
1579948	3879049	4895163	5871579	6641595	7518045
1585751	3893742	4895165	5879585	6641597	7521638
1597923	3903931	4895181	5887358	6651979	7526036
1599034	3912309	4896684	5900742	6654466	7526709
1608236	3916972	4931374	5907548	6664168	7530269
1612938	3917373	4933012	5908247	6672120	7539185
1623796	3941987	4937282	5918614	6686038	7541792
1631195	3958063	4943446	5925161	6691296	7542625
1638637	3965881	4952843	5935153	6699175	7545740
1649498	3969192	4963042	5952816	6707575	7556456
1663722	3975337	4963343	5958432	6715098	7562331
1665819	3979492	4967349	5963220	6741697	7562339
1671233	3995778	4968769	5967757	6741733	7569753
1679753	4018019	4982227	5968381	6742066	7571018
1696773	4042273	4984448	5971764	6744705	7573165
1697071	4051558	5002761	5993454	6755529	7573170
1716367	4053321	5003287	6004114	6771103	7583907
1729955	4056295	5004678	6020578	6789788	7592359

ISR Numbers					
1741139	4072000	5037056	6020838	6797743	7603188
1741141	4083763	5047776	6020839	6810362	7617757
1741153	4099224	5060759	6020841	6814318	7619647
1752278	4111296	5080368	6020847	6814540	7629401
1755356	4115429	5095826	6020856	6819127	7631177
1757106	4122165	5103378	6022285	6831146	7638223
1769776	4123160	5104731	6038203	6835646	
1778870	4123737	5105365	6038899	6857240	
1779094	4127536	5106538	6041891	6857264	
1805936	4130783	5114621	6042051	6857948	
1823289	4131601	5129229	6049294	6863407	
1834092	4142080	5131218	6053349	6875472	
1841478	4145509	5131749	6054326	6914591	
1843443	4148546	5137985	6064298	6918823	
1872034	4171660	5140293	6067984	6933504	
1921495	4173247	5159686	6074628	6939483	
1948049	4177524	5224121	6076467	6967635	
1988818	4185583	5240095	6087579	6968644	
1991919	4189065	5245474	6089105	6972286	
3014368	4199520	5252225	6094874	6972375	
3030480	4202051	5252230	6099302	6994516	
3058933	4206817	5255294	6102623	6994517	
3062769	4207996	5263463	6124204	6999141	
3070689	4210258	5280524	6153885	6999793	
3078913	4223880	5290315	6162215	7035640	
3091625	4225245	5294733	6162216	7039065	
3125034	4229154	5302109	6163128	7056890	
3163714	4235933	5311061	6183530	7060316	
3177510	4240745	5314918	6189787	7090810	
3177596	4245443	5320250	6203732	7131524	
3184624	4251830	5322057	6227349	7141194	
3186960	4252604	5331117	6282756	7142719	
3211012	4268823	5339870	6286472	7144979	
3212636	4269660	5361332	6295251	7145554	
3214965	4279340	5369467	6296187	7147892	
3218265	4301502	5370096	6296230	7166151	
3260930	4302154	5380869	6305445	7197124	
3271185	4314057	5405994	6312044	7202025	
3273469	4350921	5438877	6335525	7206733	

ISR Numbers				
3281335	4353618	5444483	6336105	7216905
3286518	4365923	5449817	6339531	7225333
3298745	4369054	5460194	6344975	7227858
3305353	4375127	5489423	6357044	7229021
3305613	4407385	5518056	6368049	7238700
3312764	4417739	5526263	6369559	7250692
3312806	4436375	5563639	6377378	7266948
3316051	4443963	5587617	6399306	7269344
3323967	4457501	5588519	6408398	7282731
3326649	4535923	5589959	6411184	7288179
3337532	4551792	5600921	6422741	7289879
3378989	4561429	5622816	6429938	7298648
3389117	4575753	5645579	6431196	7323131
3435085	4575977	5661250	6450414	7334344
3446235	4577755	5662583	6458625	7334817
3458448	4596083	5672891	6478757	7340611
3459477	4596263	5693769	6480173	7340630
3491746	4604309	5695913	6486532	7346667
3501128	4620648	5698128	6490852	7357698
3513894	4695580	5700218	6496230	7367306
3544793	4713481	5713157	6501452	7368695
3556372	4738550	5714531	6518532	7374842
3603801	4744245	5721407	6520027	7374843
3633040	4755649	5747975	6522445	7378301
3648969	4768686	5748105	6522446	7386817
3659270	4770680	5748106	6522448	7394735
3662817	4771857	5755523	6524629	7404843
3668429	4786233	5765086	6531557	7408113
3704281	4787080	5780125	6547740	7409647
3704410	4788599	5786973	6547743	7421466

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/s/

LORETTA HOLMES
08/30/2011

CAROL A HOLQUIST
08/31/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 5, 2011

TO: Debra Birnkrant M.D.
Director
Division of Anti-Viral Products (DAVP)
Office of Antimicrobial Products

John Lazor, Pharm.D.
Director, Division of Clinical Pharmacology 4
(DCP4)

FROM: Arindam Dasgupta, Ph.D., Staff Fellow
Xikui Chen, Ph.D., Chemist
Division of Bioequivalence and GLP Compliance
(DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 202-895, Darunavir
(Prezista®) Oral Suspension, Sponsored by Tibotec
Pharmaceuticals Ltd.

At the request of the Division of Antiviral Products (DAVP), and the Division of Clinical Pharmacology 4, DBGC audited the clinical and analytical portions of the following studies:

Study Number: TMC114-TiDP29-C169

Study Title: "A Phase I, open-label, randomized, crossover trial in healthy subjects to compare the oral

bioavailability of a suspension formulation of darunavir (DRV) to that of the commercial 300 mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low dose ritonavir."

Study Number: TMC114-TiDP29-C228

Study Title: "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 to < 6 years of age"

The clinical portion of Study TMC114-TiDP29-C169 was conducted at Kendle International B.V., Clinical Pharmacology Unit, Bolognalaan 40, 3584 CJ Utrecht, the Netherlands. Following inspection of the clinical site (July 18 to 22, 2011), significant problem concerning retention of study reserve samples was found, but the FDA field investigator did not issue a Form FDA-483 (see communication with the ORA field investigator in **attachment 1**).

Audit of the analytical portions of studies TMC114-TiDP29-C169 and TMC114-TiDP29-C228 were conducted at Janssen Research and Development, Turnhoutseweg 30, B2340 Beerse, Belgium and at (b) (4) respectively. Following the inspections at the two sites (Site #1: Janssen Research and Development, 7/11-15/2011, and Site #2: (b) (4)), Form FDA-483s were issued (**Attachments 2 and 3**). DBGC received the (b) (4) written response to the inspectional findings on August 3, 2011 (**Attachment 4**). DBGC is yet to receive Janssen's written response to the inspectional findings. We will amend this memorandum if the response changes our conclusion.

The 483 observations for studies TMC114-TiDP29-C169 (analytical), TMC114-TiDP29-C228 (analytical), (b) (4) written response, findings at Kendle International B.B.

Clinical Pharmacology Unit (clinical site) and our evaluations follow:

Janssen Research and Development, Beerse, Belgium (Site #1)

1. Regarding TMC114-BA-819, entitled "Validation of an LC-MS/MS method for the determination of TMC114, ritonavir, and lopinavir in human heparin plasma":

The stability evaluations for day 5 extract re-injection on August 29, 2006 in method validation TMC114-BA819 failed to use freshly-prepared calibrators or freshly-prepared references.

During the inspection, we observed that calibration standards were not prepared freshly for stability of day 5 extract re-injection. Fresh calibrators should be used for stability evaluations. However, for study samples, the longest duration from first sample injection to last sample injection in an analytical run was about 25 hours. The re-injection stability is unlikely to impact the assay results significantly.

(b) (4) (Site #2)

1. Failed to use freshly prepared calibrators in the validation of autosampler stability during the conduct of TMC114/ritonavir pre-study validations.

In their response, (b) (4) acknowledged the observation and indicated that since the study, (b) (4) has updated their procedures to use freshly prepared calibration standards for assessment of autosampler stability. (b) (4) plans to generate new data to demonstrate autosampler stability for TMC114/ritonavir using freshly prepared calibrators by August 15, 2011.

The above observation is not likely to affect the outcome of the study.

**2. Failed to document all aspects of the study conduct.
For example:**

a) Validation experiment for demonstrating autosampler stability for 21 hours in pre-study method validation for

TMC114/ritonavir failed to meet acceptance criteria. Subsequently, autosampler stability experiment was repeated and reported as acceptable. However, no investigation was documented for the failed validation experiment.

In their written response, (b) (4) acknowledged the observation and indicated that at the time of the study, (b) (4) did not have a procedure for formal investigations of unexpected laboratory results. However, since the study (December 3, 2010), a formal investigational procedure was implemented by (b) (4). Since the inspection, a retrospective investigation was conducted for the failed validation run which concluded that sample contamination during extraction was the most likely explanation for the failed result.

(b) (4) response is adequate and the above finding is not likely to impact the outcome of the current study.

b) Failure to maintain documentation for individual calibrators and QC sets used during sample processing for TMC114/ritonavir study. Calibrator and QC samples were stored as multi-use aliquots. In absence of documentation for individual calibrators or QC sets used during analysis or of their disposal, it cannot be confirmed if the calibrators and QCs used were within their validated freeze/thaw stability cycles.

(b) (4) acknowledged the observation and stated that they will implement a new labeling procedure for future studies such that individual calibrators and QCs were uniquely identified and tracked along with study samples.

The above finding is not likely to impact outcome of the current study.

3. Failure to retain the audit trail for the initial results table during data processing for TMC114/ritonavir studies. This did not allow complete reconstruction of events during data processing.

In their response, (b) (4) acknowledged the observation and indicated that they would implement new procedures where a single quantitation method would be created from default settings and would be used for processing each run in a study. Any changes made thereof was to be captured in the audit trail to allow complete reconstruction of events during data processing. To address the concerns, (b) (4)

reprocessed all their data using the modified procedure. The results of the reprocessed data were comparable to the original data. Hence the above observation is not likely to affect the outcome of the current study.

Finding at Kendle International B.V. Clinical Pharmacology Unit, Bolognaaan, Utrecht, the Netherlands (Clinical site)

During the inspection, the FDA field investigator found that the reserve samples of the test article (darunavir oral suspension) and reference standard (Darunavir 300 mg tablet) used in conducting the bioequivalence study TMC114-TiDP29-C169 were not retained as required by the bioequivalence regulations 21 CFR 320.38 and 63. Due to the absence of reserve samples, authenticity of the drug products used in the study cannot be assured. Please note that this observation should have been a Form FDA-483 observation because study TMC114-TiDP29-C169 is a pivotal bioequivalence study and retention samples for both the test and reference products should have been retained at Kendle International B.V. Clinical Pharmacology Unit (see attachment 1 for more details).

Conclusion:

Following the above inspections, DBGC recommends the following:

1. Data from the analytical portion of study TMC114-TiDP29-C169 can be used for review. However, in absence of reserve samples at the clinical site (see DBGC evaluation for inspectional finding at the clinical site and information provided in Attachment 1) the authenticity of the test and reference products used in study TMC114-TiDP29-C169 cannot be assured. Overall, DBGC recommends that the study TMC114-TiDP29-C169 not be accepted for Agency review.
2. The analytical portion for study TMC114-TiDP29-C228 can be accepted for agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Arindam Dasgupta, Ph.D.

Xikui Chen, Ph.D.

Final Classification:

Clinical

Kendle International B.V., Clinical Pharmacology Unit,
Bolognalaan 40, 3584 CJ Utrecht, the Netherlands - VAI

Analytical

Janssen Research and Development, Turnhoutseweg 30, B2340
Beerse, Belgium - VAI

(b) (4)

cc: DARRTS
OSI/Ball
DBGC/Salewski/Haidar/Ball/Yau/Viswanathan/Dasgupta/Chen/
Djernett/CF
OC/CDER/OND/OAP/DAVP/Birnkrant/Linda C. Onaga
OTS/OCP/DCPIV/Lazor/Stanley Au
HFR-CE350/Jonee Mearns
HFR-CE4550/Karen Bryerton-Cooper

Draft: XC 8/4/11

Draft: AD 8/5/11

Edit: MKY 8/5/11

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cc: email

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/s/

XIKUI CHEN
08/05/2011

ARINDAM DASGUPTA
08/05/2011

MARTIN K YAU
08/05/2011

SAM H HAIDAR
08/05/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA #202895 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Prezista Established/Proper Name: darunavir Dosage Form: oral suspension Strengths: 100 mg/mL		
Applicant: Tibotec, Inc. Agent for Applicant (if applicable):		
Date of Application: March 29, 2011 Date of Receipt: March 30, 2011 Date clock started after UN:		
PDUFA Goal Date: September 30, 2011		Action Goal Date (if different):
Filing Date: May 27, 2011		Date of Filing Meeting: April 29, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3 - NewDosage Form		
Proposed indication(s)/Proposed change(s): To include a new dosage form (oral suspension) and expand the treatment population to 3 years of age and older		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? No <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input checked="" type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input checked="" type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 062,477				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?					
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].					
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?					
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			x		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p> <p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>		X		

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the</i>				

<p><i>original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic submission

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	x			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	x			
<p>If studies or full waiver not included, is a request for full</p>				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	X			
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (PEPFAR carton and container labels)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Yes sent on 4/28/11
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Yes sent on 4/28/11
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Yes sent on 4/28/11
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			DSI consult for BE audit for international site sent 4/27/11
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):		X		

<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 29, 2011

BLA/NDA/Supp #: 202895

PROPRIETARY NAME: Prezista

ESTABLISHED/PROPER NAME: darunavir

DOSAGE FORM/STRENGTH: 100 mg/mL oral suspension

APPLICANT: Tibotec, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of HIV-1 Infection

BACKGROUND:

Tibotec has submitted an original NDA for Prezista oral suspension formulation for the treatment of HIV-1 infection. This NDA is in response to the following:

- Written Request for Pediatric studies issued under NDA 21-976 (November 17, 2006 amended August 16, 2007),
- PREA PMR 389-1 (Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients less than 6 years of age. Please evaluate dose requirements and safety in pediatric patients less than 6 years of age with HIV-1 infection after preliminary review of data from the 6 to 17 year olds in trial TMC114-C212 with the Division of Antiviral Products (DAVP)) issued under NDA 21-976/S-006.
- PMR 389-2 (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 issued under NDA 21-976/S-006.

This original NDA provides PK, Safety, tolerability and virologic response data that supports weight-based dosing recommendations of Prezista in combination with ritonavir for treatment experienced HIV-1 pediatric patients 3 to <6 years. The application provides new oral dose form that is suitable for achieving weight based dose adjustment. Tibotec updated the current Prezista labeling to include dosing recommendations for age groups 3 to <6 years.

In addition, the final study report to fulfill PMR 389-2, issued under NDA 21-976/S-006, a partial waiver of pediatric studies for the oral suspension and a request for pediatric and 3-year Waxman-Hatch exclusivity.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Linda C. Onaga, MPH	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Yodit Belew, MD		Y
Clinical	Reviewer:	Regina Alivisatos, MD	Y
	TL:	Yodit Belew, MD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Lisa Naeger, PhD	Y
	TL:	Jules O'Rear, PhD	N
Clinical Pharmacology	Reviewer:	Stanley Au, PharmD	Y
	TL:	Sarah Robertson, PharmD	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Peyton Myers, PhD	Y
	TL:	Hanan Ghantous, PhD, DABT	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Mark Seggel, PhD	N
	TL:	Steve Miller, PhD	N

Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Pharmacometrics	Reviewer:	Kevin Krudys, PhD	Y
	TL:	Pravin Jadhav, PhD	N
CMC Biopharmaceutical Reviewer	Mark Seggel		N
OSE Project Manager	Brantley Dorch		Y
Other Attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
--	---

<p>If yes, list issues:</p>	
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: BA studies used to support application.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
CLINICAL MICROBIOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
IMMUNOGENICITY (BLAs/BLA efficacy supplements only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<u>Environmental Assessment</u>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
If no, was a complete EA submitted?	<input type="checkbox"/> YES <input type="checkbox"/> NO

<p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDA/NDA supplements only) <p>Comments: Consult went out on April 20, 2011 Due June 15, 2011</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: Six out of the seven sites were found acceptable at the time of the filing meeting.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Jeffrey Murray, MD, MPH, Deputy Director</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/> The application is unsuitable for filing. Explain why:	

<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]</p>
<input type="checkbox"/>	Other

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

/s/

LINDA C ONAGA
08/05/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 26, 2011

To: Linda Onaga, MPH – Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: DDMAC comments on draft Prezista Oral Suspension Patient
Information (PPI)
NDA 202895

This consult is in response to DAVP's April 28, 2011, request for DDMAC review of the draft Prezista Oral Suspension labeling.

Comments on the proposed prescribing information (PI) and carton and container labeling will be provided under separate cover.

Our comments are provided directly below in the proposed Med Guide provided by the DAVP eRoom on July 25, 2011.

DDMAC appreciates the opportunity to provide comments. If you have any questions, please contact Michelle Safarik at 301-796-0620 or at michelle.safarik@fda.hhs.gov.

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

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

/s/

MICHELLE L SAFARIK
07/26/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202895

Name of Drug: Prezista (darunavir) oral suspension

Applicant: Tibotec, Inc

Labeling Reviewed

Submission Date: March 29, 2011

Receipt Date: March 30, 2011

Background and Summary Description

Tibotec has submitted a NDA for Prezista oral suspension for the treatment of HIV-1 infection. This NDA is in response to the Written Request for Pediatric studies issued under NDA 21-976 (November 17, 2006 amended August 16, 2007). The NDA provides pharmacokinetic, safety, tolerability and virologic response data that supports weight-based dosing recommendations of Prezista in combination with ritonavir for treatment experienced HIV-1 pediatric patients 3 to less than 6 years. This application also provides new oral dose form that is suitable for achieving weight based dose adjustments. Tibotec updated the current Prezista labeling to include dosing recommendations for age groups 3 to <6 years.

Tibotec submitted a waiver of pediatric studies in patients (b) (4) years of age and a request for pediatric exclusivity.

The labeling (in SPL format) was submitted electronically to the NDA.

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an "X."

Recommendations

In addition, the following labeling issues were identified:

1. Highlights Overview:
 - a. 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 and Major Changes:
 - a. Contraindications (4) 4/2010 should be removed since it one year after date of the labeling change.
 - b. Please remove extra bullet under Warning and Precautions.
3. Dosage Forms and Strengths
 - a. Place the dosage forms on two different lines and add bullets at the beginning of each
 - 100 mg/mL oral suspension
 - 75mg tablets, 150 mg tablets, 400 mg tablets and 600 mg tablets
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) [REDACTED]” from the Highlights section and replace with “Pregnancy registry available. (8.1)”
6. Full Prescribing Information: Contents*
 - a. Under 6.4, indent the second line of text.
 - b. Section 13.1 should be listed as, “Carcinogenesis, mutagenesis, impairment of fertility”
7. Full Prescribing Information
 - 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.
 1. 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*.
8. Patient Package Insert
 - a. 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.

All labeling issues identified on the following pages with an “X” and identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by June 10, 2011. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager Date

Chief, Project Management Staff Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading - if no contraindications are known, it must state "None")
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)

<ul style="list-style-type: none">• Patient Counseling Information Statement (required statement)
<ul style="list-style-type: none">• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) – 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ removal 2/2010.”
- **Indications and Usage**
 - If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.
- **Contraindications**
 - This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
 - All contraindications listed in the FPI must also be listed in HL.
 - List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
 - For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.
- **Adverse Reactions**
 - Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
 - For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.
- **Patient Counseling Information Statement**
 - Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”
- **Revision Date**
 - A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed

discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

LINDA C ONAGA
06/20/2011

KAREN D WINESTOCK
06/23/2011

Pediatric Exclusivity Board Minutes

June 7, 2011

Voting Board Members

John Jenkins, Chair
Sally Loewke
Dena Hixon
Norman Stockbridge

Review Division/Office

Jiang Liu
Stanley Au
Linda Onaga
Yodit Belew

Others

Matthew Bacho, Board RPM
Rosemary Addy
Alyson Karesh
Virginia Elgin
Yeruk Mulugeta
Benjamin Ortiz

Advisors

Kim Dettelbach
William Rodriguez
Martha Nguyen

Determination for Darunavir (NDA 202895/S-000)

Initial Written Request:	11/17/06
Amended Written Requests:	8/16/07
Timeframe for submission of studies:	12/31/11
Date report of studies received:	6/20/08 & 3/30/11
Due Date for Pediatric Exclusivity Determination:	6/28/11

The Written Request (WR), as amended, described two (2) studies to provide data on the use of darunavir for the treatment of HIV infection in pediatric patients.

1. Tibotec (Sponsor) submitted reports on the following pivotal studies:
 - Study 1 (C212) – A Phase 2, open-label trial to investigate pharmacokinetics, safety, tolerability and antiviral activity of TMC114/rtv b.i.d. in treatment-experienced HIV-1 infected children and adolescents (ages 6 to < 18); and
 - Study 2 (TiDP29-C228) – A Phase 2, 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 to < 6 years of age.
2. In response to inquiries from the Board, the Review Division (Division) made the following points:
 - The report for Study 1 was received on 6/20/08 [NDA 021976/S-009] while the latest submission of Study 2 in children 3 to < 6 years of age was received on 3/30/11;
 - The review of Study 1 resulted in labeling for children 6 to < 18 years of age [approved on 12/18/08];
 - The lower age limit for children studied under this WR was moved from 1 month to 3 years because of seizure cases resulting in death;
 - Tablets, 75 and 150 mg, were used in the older kids and an oral suspension (100 mg/ml) was developed for the younger age group;
 - The pediatric safety profile was similar to adults;

- The Division received the 24-week analysis for Study 2 and expected a 48-week analysis to be submitted later;
 - The studies were not sufficiently powered to show efficacy but it could be extrapolated from adults;
 - Virologic failure (resistance) was seen in these studies and similar to the same in adults.
3. The Board Chair asked the Office of Chief Counsel [REDACTED] (b) (5) [REDACTED] noted that thi [REDACTED] 1. OCC (b) (5) [REDACTED]
4. The Chair asked if a sufficient number of patients had been enrolled into each age group. The Division noted the difficulty of enrolling younger children in this context and was satisfied with the Sponsor's effort. The Chair cautioned the Division to be more specific about the minimum number of patients in future WRs since, in this case, the language would have allowed the Sponsor to enroll whoever they wanted, e.g., only adolescents.
5. The Chair also drew attention to the use of equivocal language in those sections pertaining to safety and pharmacokinetics (PK). The Division stated that their current WRs address the latter by specifying the variability requirements of such studies.
6. When asked about the data used to support a suitable dose, the Division noted that they had a sufficient number of patients, along with older children and adults, to determine an exposure response.
7. The Chair pointed out the contradiction between the minimum number of patients for each age group in the PK study (between 6 and 12) and a later statement requiring approximately even distribution across all age groups.
8. The Chair recommended that the Division carefully review their pending WRs for the kind of vague language used in this instance and, if necessary, ask the Pediatric Review Committee for assistance.

Recommendations

1. The Board agreed that the Sponsor fairly responded to the WR.
2. Pediatric Exclusivity was granted effective June 7, 2011 (see Checklist signed into DARRTS).
3. The Division will inform the Sponsor via email, utilizing a notification script that Pediatric Exclusivity was granted. The fact that exclusivity was granted will be posted on the pediatric web site along with the WR and any amendments as required by FDAAA (2007), and the exclusivity will be reflected in the next monthly update to the Orange Book.

Prepared by: _____

Date: _____

Board Chair: _____

Date: _____

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/s/

MATTHEW A BACHO
06/17/2011

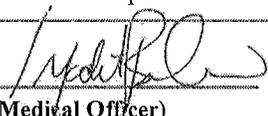
JOHN K JENKINS
10/26/2011

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

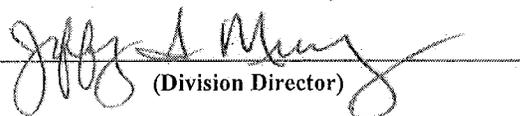
PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA: 11/17/2006 (amended 08/16/2007)
 Application Written Request was made to: NDA/BLA/IND# IND 62,477/NDA 21-976
 Timeframe Noted in Written Request for Submission of Studies: before 12/31/2011
 NDA/BLA# 21-976, 202-895 Supplement # N/A Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
 Sponsor Tibotec
 Generic/Non-proprietary Name: Darunavir Tradename: Prezista
 Strength 75mg, 150mg, 400 mg, and 600 mg tablets
 100 mg/ml oral suspension
 Dosage Form/Route: Solution and tablets per os (orally)
 Date of Receipt of Reports of Studies 06/20/2008 and 03/29/2011
 Pediatric Exclusivity Determination Due Date (90 or 180 days from the date of studies receipt): 06/28/11

Was a formal Written Request made for the pediatric studies submitted?	Y X	N ___
Were the studies submitted after the Written Request?	Y X	N ___
Were the reports submitted as a supplement or amendment to an NDA/BLA, or original NDA/BLA?	Y X	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y X	N ___
Were the studies conducted in accordance with commonly accepted scientific principles and protocols?	Y X	N ___
Did the studies fairly respond to the Written Request?	Y X	N ___

SIGNED Regina Alivisatos, MD 
 (Reviewing Medical Officer)

DATE 05/02/2011

SIGNED 
 (Division Director)

DATE 5/18/2011

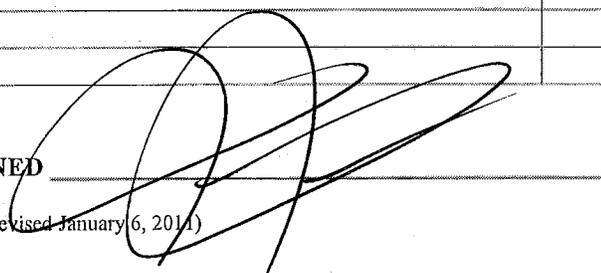
Do not enter in DARRTS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD via Pediatric and Maternal Health Staff PM

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **Granted** **Denied**

Existing Patent or Exclusivity Protection: See Attachment

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date

SIGNED 
 (Last revised January 6, 2011)

DATE 6/7/11

1. Unexpired Patents for Prezista (darunavir ethanolate) Tablet; Oral; EQ 300 mg Base

NDA #	Product #	Patent #	Expiration	DSC	DPC	Use Code	Delist Request
021976	001	5843946	12/1/15	-	Yes	U-744 U-903 U-935	-
-	-	6037157	6/26/16	-	-	U-935	-
-	-	6248775	8/13/14	Yes	-	-	-
-	-	6335460	8/25/12	Yes	Yes	U-744 U-903 U-935	-
-	-	6703403	6/26/16	-	-	U-935	-
-	-	7470506	6/23/19	-	-	U-935	-
-	-	7700645	12/26/26	Yes	Yes	-	-

DSC: Drug Substance Claim

DPC: Drug Product Claim

U-744: TREATMENT OF HIV INFECTION IN ANTIRETROVIRAL TREATMENT-EXPERIENCED ADULT PATIENTS

U-903: TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN ADULT PATIENTS

U-935: TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN ADULT PATIENTS, AND TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN PEDIATRIC PATIENTS 6 YEARS OF AGE AND OLDER

Unexpired Exclusivity for Prezista (darunavir ethanolate) Tablet; Oral; EQ 300 mg Base

NDA #	Product #	Code	Expiration	Definition
021976	001	D-119	12/18/11	DOSING RECOMMENDATIONS FOR HIV INFECTED PEDIATRIC PATIENTS 6 TO LESS THAN 18 YEARS OF AGE
-	-	D-129	12/13/13	800/100 MG DARUNAVIR/RITONAVIR, ONCE DAILY, IN TREATMENT -EXPERIENCED HIV-1 INFECTED PATIENTS WITH NO DARUNIVIR RESISTANCE ASSOCIATED SUBSTITUTIONS
-	-	I-578	10/21/11	EXPANSION OF INDICATION TO INCLUDE TREATMENT OF HIV IN TREATMENT NAIVE ADULTS
-	-	NCE	6/23/11	NEW CHEMICAL ENTITY

2. Unexpired Patents for Prezista (darunavir ethanolate) Tablet; Oral; EQ 600 mg Base

NDA #	Product #	Patent #	Expiration	DSC	DPC	Use Code	Delist Request
021976	002	5843946	12/1/15	-	Yes	U-744 U-903 U-935	-
-	-	6037157	6/26/16	-	-	U-935	-
-	-	6248775	8/13/14	Yes	-	-	-

-	-	6335460	8/25/12	Yes	Yes	U-744 U-903 U-935	-
-	-	6703403	6/26/16	-	-	U-935	-
-	-	7470506	6/23/19	-	-	U-935	-
-	-	7700645	12/26/26	Yes	Yes	-	-

DSC: Drug Substance Claim

DPC: Drug Product Claim

U-744: TREATMENT OF HIV INFECTION IN ANTIRETROVIRAL TREATMENT-EXPERIENCED ADULT PATIENTS

U-903: TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN ADULT PATIENTS

U-935: TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN ADULT PATIENTS, AND TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN PEDIATRIC PATIENTS 6 YEARS OF AGE AND OLDER

Unexpired Exclusivity for Prezista (darunavir ethanolate) Tablet; Oral; EQ 600 mg Base

NDA #	Product #	Code	Expiration	Definition
021976	002	D-119	12/18/11	DOSING RECOMMENDATIONS FOR HIV INFECTED PEDIATRIC PATIENTS 6 TO LESS THAN 18 YEARS OF AGE
-	-	D-129	12/13/13	800/100 MG DARUNAVIR/RITONAVIR, ONCE DAILY, IN TREATMENT -EXPERIENCED HIV-1 INFECTED PATIENTS WITH NO DARUNIVIR RESISTANCE ASSOCIATED SUBSTITUTIONS
-	-	I-578	10/21/11	EXPANSION OF INDICATION TO INCLUDE TREATMENT OF HIV IN TREATMENT NAIVE ADULTS
-	-	NCE	6/23/11	NEW CHEMICAL ENTITY

3. Unexpired Patents for Prezista (darunavir ethanolate) Tablet; Oral; EQ 400 mg Base

NDA #	Product #	Patent #	Expiration	DSC	DPC	Use Code	Delist Request
021976	003	5843946	12/1/15	-	Yes	U-744 U-903 U-935	-
-	-	6037157	6/26/16	-	-	U-935	-
-	-	6248775	8/13/14	Yes	-	-	-
-	-	6335460	8/25/12	Yes	Yes	U-903 U-935	-
-	-	6703403	6/26/16	-	-	U-935	-
-	-	7470506	6/23/19	-	-	U-935	-
-	-	7700645	12/26/26	Yes	Yes	-	-

DSC: Drug Substance Claim

DPC: Drug Product Claim

U-744: TREATMENT OF HIV INFECTION IN ANTIRETROVIRAL TREATMENT-EXPERIENCED ADULT PATIENTS

U-903: TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN ADULT PATIENTS

U-935: TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN ADULT PATIENTS, AND TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN PEDIATRIC PATIENTS 6 YEARS OF AGE AND OLDER

Unexpired Exclusivity for Prezista (darunavir ethanolate) Tablet; Oral; EQ 400 mg Base

NDA #	Product #	Code	Expiration	Definition
021976	003	D-118	10/21/11	TWO 400MG TABLETS ONCE DAILY, CO-ADMINISTERED WITH 100MG RITONAVIR
-	-	D-119	12/18/11	DOSING RECOMMENDATIONS FOR HIV INFECTED PEDIATRIC PATIENTS 6 TO LESS THAN 18 YEARS OF AGE
-	-	D-129	12/13/13	800/100 MG DARUNAVIR/RITONAVIR, ONCE DAILY, IN TREATMENT -EXPERIENCED HIV-1 INFECTED PATIENTS WITH NO DARUNIVIR RESISTANCE ASSOCIATED SUBSTITUTIONS
-	-	I-578	10/21/11	EXPANSION OF INDICATION TO INCLUDE TREATMENT OF HIV IN TREATMENT NAIVE ADULTS
-	-	NCE	6/23/11	NEW CHEMICAL ENTITY

4. Unexpired Patents for Prezista (darunavir ethanolate) Tablet; Oral; EQ 75 mg Base

NDA #	Product #	Patent #	Expiration	DSC	DPC	Use Code	Delist Request
021976	004	5843946	12/1/15	-	Yes	U-935	-
-	-	6037157	6/26/16	-	-	U-935	-
-	-	6248775	8/13/14	Yes	-	-	-
-	-	6335460	8/25/12	Yes	Yes	U-935	-
-	-	6703403	6/26/16	-	-	U-935	-
-	-	7470506	6/23/19	-	-	U-935	-
-	-	7700645	12/26/26	Yes	Yes	-	-

DSC: Drug Substance Claim

DPC: Drug Product Claim

U-935: TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN ADULT PATIENTS, AND TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN PEDIATRIC PATIENTS 6 YEARS OF AGE AND OLDER

Unexpired Exclusivity for Prezista (darunavir ethanolate) Tablet; Oral; EQ 75 mg Base

NDA #	Product #	Code	Expiration	Definition
021976	004	D-119	12/18/11	DOSING RECOMMENDATIONS FOR HIV INFECTED PEDIATRIC PATIENTS 6 TO LESS THAN 18 YEARS OF AGE
-	-	D-129	12/13/13	800/100 MG DARUNAVIR/RITONAVIR, ONCE DAILY, IN TREATMENT -EXPERIENCED HIV-1 INFECTED PATIENTS WITH NO DARUNIVIR RESISTANCE ASSOCIATED SUBSTITUTIONS
-	-	NS	12/18/11	NEW STRENGTH

5. Unexpired Patents for Prezista (darunavir ethanolate) Tablet; Oral; EQ 150 mg Base

NDA #	Product #	Patent #	Expiration	DSC	DPC	Use Code	Delist Request
021976	005	5843946	12/1/15	-	Yes	U-935	-
-	-	6037157	6/26/16	-	-	U-935	-
-	-	6248775	8/13/14	Yes	-	-	-
-	-	6335460	8/25/12	Yes	Yes	U-935	-
-	-	6703403	6/26/16	-	-	U-935	-
-	-	7470506	6/23/19	-	-	U-935	-
-	-	7700645	12/26/26	Yes	Yes	-	-

DSC: Drug Substance Claim

DPC: Drug Product Claim

U-935: TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN ADULT PATIENTS, AND TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN PEDIATRIC PATIENTS 6 YEARS OF AGE AND OLDER

Unexpired Exclusivity for Prezista (darunavir ethanolate) Tablet; Oral; EQ 150 mg Base

NDA #	Product #	Code	Expiration	Definition
021976	005	D-119	12/18/11	DOSING RECOMMENDATIONS FOR HIV INFECTED PEDIATRIC PATIENTS 6 TO LESS THAN 18 YEARS OF AGE
-	-	D-129	12/13/13	800/100 MG DARUNAVIR/RITONAVIR, ONCE DAILY, IN TREATMENT -EXPERIENCED HIV-1 INFECTED PATIENTS WITH NO DARUNIVIR RESISTANCE ASSOCIATED SUBSTITUTIONS
-	-	NS	12/18/11	NEW STRENGTH

6. Discontinued Drug Products Listing of Unexpired Patents & Exclusivity for Prezista (darunavir ethanolate) – None

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/s/

MATTHEW A BACHO
06/07/2011

JOHN K JENKINS
06/07/2011

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 12, 2011

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

FROM: Martin K. Yau, Ph.D.
Acting Team Leader—Bioequivalence
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations

SUBJECT: FY 2011, **High Priority CDER NDA Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 202-895
DRUG: Darunavir (Prezista®) Oral Suspension
SPONSOR: Tibotec Pharmaceuticals Ltd.

This memorandum requests the inspection of the clinical portion of the study below. The analytical portion was already requested in the previous memorandum stamped in DARRTS on May 10, 2011. **Due to the 'User Fee' due date, the inspection should be completed before July 29, 2011.**

Study/Protocol TMC114-TiDP29-C169 (N = 23):

"A Phase I, open-label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of darunavir (DRV) to that of the commercial 300 mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low dose ritonavir."

Clinical Site: [currently not operational]
Kendle International B.V.
Clinical Pharmacology Unit
Bolognalaan 40
3584 CJ Utrecht
The Netherlands

Clinical

Investigator: S. Spinosa Guzman

Contact Point: Angela A.M.C. Claessens M.D. Ph.D.
General Manager, The Netherlands & Belgium
Kendle International B.V.
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3562 GB Utrecht
The Netherlands
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The clinical study site is not operational at this time. The clinical study contractor, Kendle International informed the review division that the clinical trial records are available for inspection at a nearby archiving facility in Utrecht, The Netherlands.

Please audit the records of all study subjects enrolled in the study site. The subject records in the FDA submission should be compared to the original documents at the reserved facility. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to adverse events, concomitant medications (including ritonavir), inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Please confirm the presence of 100% of the signed and dated informed consent forms, and comment on this informed consent check in the EIR. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings. **Please also address the following issues during the inspection and discussed in the EIR:**

- Dosing logs must be checked to confirm that correct doses of the correct products were administered to the subjects in each treatment. It is noted that there are 4 treatments in 2 parts of the study (Part 1 for single dose pharmacokinetic data collection: Treatments A [reference], B [fasted condition], and C [fed condition]; Part 2 for multiple dose

pharmacokinetic data collection: Treatment D [fed condition]). It is also noted that ritonavir was administered in all Treatments. Please collect a copy of the randomization schedule for treatment of subject enrolled at the study site. Include a copy of site randomization schedule in the EIR.

- Please check the batch numbers of the test and reference products used in the study with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Part 320.38. The site conducting the study is responsible for randomly selecting and retaining reserve samples from the shipments of drug products provided for subject dosing. Please refer to the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) and CDER's guidance document "Handling & Retention of BA and BE Testing Samples" (<http://www.fda.gov/cder/guidance/5522fnl.pdf>) for more information. Samples of the test and reference formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg.
1114 Market Street, Room 1002
St. Louis, MO 63101

As Kendle International B.V. is currently not operational, the treatment randomization schedule and reserve samples must have been in the possession at the archiving facility. The archiving facility must be independent of the sponsor, manufacturer, or packager.

Also, obtain a written assurance from the clinical investigator or the responsible person at the study site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected

and shipped them to DPA under current program directives.
Please see the IOM and/or contact your district or DDFI for
assistance with the Sample Collection Report.

Following identification of the investigator, background
material will be forwarded directly.

Headquarters Contact Person: Michael F. Skelly, Ph.D.
(301)-796-3375

CC:
CDER DSI PM TRACK
DSI/Skelly/Dasgupta/Dejernett/Lee/CF
HFC-130/ORA HQ DFFI IOB BIMO
DCP3/Lazor/Au
HFD-530/Onaga (DAVP)
Draft: JIL 5/12/11
Edit: MFS 5/12/11; MKY 5/12/11
DSI: 6214 O:\\BE\\assigns\\bio202895.doc
FACTS: 1285589

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/s/

JANG IK LEE
05/12/2011

MARTIN K YAU
05/12/2011

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 9, 2011

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

FROM: Martin K. Yau, Ph.D.
Acting Team Leader—Bioequivalence
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations

SUBJECT: FY 2011, **High Priority CDER NDA Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 202-895
DRUG: Darunavir (Prezista®) Oral Suspension
SPONSOR: Tibotec Pharmaceuticals Ltd.

This memorandum requests inspection of the analytical portions of the two studies listed below. **Due to the 'User Fee' due date, the inspection should be completed before July 29, 2011.**

Study/Protocol TMC114-TiDP29-C169 (N = 23):

"A Phase I, open-label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of darunavir (DRV) to that of the commercial 300 mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low dose ritonavir."

Analytical Site: Janssen Research and Development
Turnhoutseweg 30,
B2340 Turnhout, Belgium

Bioanalytical Investigator: Vera Hillewaert
Phone: 32 14605820
Fax: 32 14605110
E-mail: vhillewa@its.jnj.com

Analytical Method: LC-MS/MS (for both darunavir and ritonavir)

Study/Protocol TMC114-TiDP29-C228 (N = 27):

"A Phase II, open-label trial to evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV in combination with low dose ritonavir (DRV/r) in treatment-experienced HIV-1 infected children from 3 to < 6 years of age"

Analytical Site:

(b) (4)

Bioanalytical Investigator:

(b) (4)

Contact Person:

(b) (4)

Analytical Method: LC-MS/MS (for both darunavir and ritonavir)

All pertinent items related to the LC-MS/MS method used in each analytical site for the measurement of darunavir and ritonavir concentrations in plasma should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submissions should be compared with the original documents at the site. **The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content. It is noted that Janssen and (b) (4) developed and validated the assay methods separately.

Following identification of the investigator background material will be forwarded directly. **A DSI scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise.**

Page 3 - BIMO Assignment, NDA 202-895 Darunavir (Prezista®) Oral
Suspension

Headquarters Contact Person: Michael F. Skelly, Ph.D.
(301)-796-3375

cc:

CDER DSI PM TRACK

DSI/Skelly/Dasgupta/Dejernett/Lee/CF

HFC-130/ORA HQ DFFI IOB BIMO

DCP3/Lazor/Au

HFD-530/Onaga (DRUP)

Draft: JIL 5/9/11

Edit: MKY 5/9/11

DSI: 6214 O:\\BE\\assigns\\bio202895.doc

FACTS: 1285589

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/s/

JANG IK LEE
05/10/2011

MARTIN K YAU
05/10/2011