

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205395Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205395

SUPPL #

HFD # 530 (DAVP)

Trade Name: PREZCOBIX

Generic Name: darunavir and cobicistat

Applicant Name: Janssen Products, LP

Approval Date, If Known: January 29, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

The sponsor submitted BA and BE study data in healthy volunteers, and data from a single-arm, open label study in patients with HIV-1 infection. The BA study, TMC114IFD1001, evaluated two different formulations of darunavir/cobicistat FDC formulations compared to darunavir co-administered with ritonavir. The BE study, TMC114FD1003, evaluated the BE of the darunavir/cobicistat FDC tablet compared to the individual cobicistat and darunavir tablets. The BE data was considered pivotal and required for approval.

The open label study, GS-US-216-0130, evaluating the safety and efficacy of the darunavir/cobicistat FDC was reviewed to support the safety of the product, but was not needed for approval.

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

d) Did the applicant request exclusivity?

YES NO

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

3 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 21976 Prezista (darunavir), Tablet, Film-coated

NDA# 202895 Prezista (darunavir), Suspension

NDA# 203100 Stribild (elvitegravir, cobicistat, emtricitabine, tenofivir disoproxil fuamrate), Tablet

NDA# 203094 Tybost (cobicistat), Tablet

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

Cobicistat co-administered with darunavir was approved in September 2014. The only data essential to the approval of the fixed-dose formulation of darunavir and cobicistat is the bioequivalence study, TMC1141FD1003.

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

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

Investigation #1 !
!
YES ! NO
! Explain:

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

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

Investigation !
!

YES
Explain:

! NO
! Explain:

Investigation #2

!
!

YES
Explain:

! NO
! Explain:

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

YES NO

If yes, explain:

=====

Name of person completing form: Nina Mani, PhD, MPH
Title: Regulatory Project Manager
Date: December 24, 2014

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

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

NINA MANI
01/29/2015

JEFFREY S MURRAY
01/29/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 205395 BLA #	NDA Supplement # 0 BLA Supplement #	If NDA, Efficacy Supplement Type: n/a <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Prezcobix Established/Proper Name: darunavir and cobicistat Dosage Form: Tablets, 800mg/150mg		Applicant: Janssen Products, LP Agent for Applicant (if applicable):
RPM: Nina Mani		Division: Antiviral Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:
Note: 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.		
Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>January 31, 2015</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
❖ 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 _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 4
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <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 |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other HIV List serve
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
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 (including approval letter with final labeling)	Action(s) and date(s): AP and 1/29/2015
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (indicate date(s)):	5/27/2014
• Review(s) (indicate date(s)):	5/20/2014
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> 1/28/2015 DMEPA: <input type="checkbox"/> 11/6/2014; 12/19/2014; 12/24/2014 DMPP/PLT (DRISK): <input type="checkbox"/> 1/5/2015 OPDP: <input type="checkbox"/> 1/5/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	5/30/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<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
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>December 3, 2014</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
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 1/2/2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None Three (3)
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	12/22/2014
<ul style="list-style-type: none"> • 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>)	In Clinical Review/ 12/19/2014 and 12/22/2014
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 12/15/2014
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A

❖ Risk Management	
<ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<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>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI 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"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/22/2014
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
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"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/23/2014
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested 12/5/2014
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) Supervisory Review(s) (<i>indicate date for each review</i>) Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review <input checked="" type="checkbox"/> No separate review <input type="checkbox"/> None 12/24/2014
❖ 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
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI 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"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None Chemistry: 12/16/2014 Biopharmaceutics: 12/5/2014
❖ Microbiology Reviews		<input type="checkbox"/> Not needed Assessment of Microbial Limits: 7/16/ 2014
<input 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 (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ 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 type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		12/17/2014
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: 9/4/2014 <input checked="" type="checkbox"/> Acceptable (In Chemistry Review) <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(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)

⁵ 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.

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

From: Mani, Nina
To: ["Gerry, Karen \[JRDCA\]"](#)
Subject: RE: NDA 205395- labeling comment
Date: Tuesday, January 27, 2015 4:33:00 PM

Hi Karen.

In Table 2 of the USPI, the sedative/hypnotics medications that are listed should not be spaced out (buspirone, diazepam, etc, parenterally administered midazolam and zoldipem). Please follow the spacing in the Word version since it appears that conversion to PDF messes up the spacing.

Thanks,
Nina

From: Gerry, Karen [JRDCA] [mailto:kgerry@its.jnj.com]
Sent: Tuesday, January 27, 2015 2:55 PM
To: Mani, Nina
Subject: RE: NDA 205395

Hi Nina,

Janssen acknowledges receipt of the appended NDA 205395 labeling comments from the Division.

Kind regards,

Karen

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/s/

NINA MANI
01/27/2015

From: Mani, Nina
To: [Gerry, Karen \[JRDCAL \(kgerry@its.jnj.com\)\]](mailto:kgerry@its.jnj.com)
Subject: NDA 205395
Date: Tuesday, January 27, 2015 2:31:00 PM
Attachments: [PREZCOBIX-annot-labeling-1_27_2015.pdf](#)
[PREZCOBIX-annot-labeling-1_27_2015.docx](#)

Hi Karen:

Kindly acknowledge receipt of the attached PDF and Word versions of the labeling for your comments.

Please accept the changes you concur with, and only leave in changes/comments that are under negotiation.

Please submit your response before **COB, Wednesday, January 28, 2015**.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
01/27/2015

From: Mani, Nina
To: "[Gerry, Karen \[JRDCA\]](#)"
Subject: RE: NDA 205395: Labeling- Section 16
Date: Friday, January 23, 2015 2:12:00 PM

If you do not concur please provide your reasoning.

From: Mani, Nina
Sent: Friday, January 23, 2015 2:07 PM
To: 'Gerry, Karen [JRDCA]'
Subject: RE: NDA 205395: Labeling- Section 16

Hi Karen:

We have the following additional edit in the Full Prescribing Information, Section 16 "How Supplied/Storage and Handling":

PREZCOBIX (darunavir and cobicistat) tablets, 800mg/150 mg, are supplied as pink, oval-shaped, film-coated tablets debossed with "800" on one side and "TG" on the other side.

If you concur with this presentation please add it in the next iteration of the labeling that you submit.

Kindly acknowledge receipt of this communication.

Regards,
Nina

From: Gerry, Karen [JRDCA] [<mailto:kgerry@its.inj.com>]
Sent: Friday, January 23, 2015 9:09 AM
To: Mani, Nina
Subject: RE: NDA 205395: Labeling

Good morning Nina,

Janssen acknowledges receipt of the additional NDA 205395 labeling comments.

Kind regards,

Karen

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: January-23-15 8:11 AM
To: Gerry, Karen [JRDCA]

Subject: NDA 205395: Labeling

Hi Karen:

Kindly acknowledge receipt of the attached labeling (Word and PDF) with our comments. When providing your response, please accept all edits we have agreement on. Only leave in edits/changes that are still being negotiated.

Please provide your response by Monday, January 26, 2015.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
01/23/2015

From: [Gerry, Karen \[JRDCA\]](#)
To: [Mani, Nina](#)
Subject: RE: NDA 205395
Date: Friday, January 16, 2015 4:02:14 PM
Attachments: [emfinfo.txt](#)

Hi Nina,

Janssen acknowledges receipt of this latest set of comments on the labeling and container label for NDA 205395.

Kind regards,

Karen

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: January-16-15 2:25 PM
To: Gerry, Karen [JRDCA]
Subject: NDA 205395

Hi Karen:

Kindly acknowledge receipt of our latest comments on the **labeling and container label**, which is based on the naming conventions we used:

- darunavir and cobicistat (for the FDC)
- darunavir coadministered with cobicistat (or ritonavir) for use of the single entities.

I am attaching both PDF and Word versions of the labeling.

In the **container label** please change:

- (b) (4) to “darunavir and cobicistat”

Please provide us with the requested changes by Wednesday, January 21, 2015.

Thanks,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002

Phone: 240-402-0333

Fax: 301-796-9883

e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
01/16/2015

From: Mani, Nina
To: "[Gerry, Karen \[JRDCA\]](#)"
Subject: RE: NDA 205395 (darunavir/cobicistat FDC)
Date: Friday, January 09, 2015 1:48:00 PM

Hi Karen:

Please submit ASAP the revised set of specifications that include all of the changes made to-date.

Thanks,
Nina

From: Gerry, Karen [JRDCA] [mailto:kgerry@its.jnj.com]
Sent: Friday, January 09, 2015 11:21 AM
To: Mani, Nina
Subject: NDA 205395 (darunavir/cobicistat FDC)
Importance: High

Good morning Nina,

Janssen is seeking the Division's advice in managing a CMC documentation oversight that has just been recognized by our CMC colleagues.

As background, during the course of review several changes to drug product specifications updates were provided to the Division and included in our responses to comments from the Agency. Below is a list of the submissions that included specification changes and the reasons for the changes:

- SN0009: Inclusion of microbiological purity acceptance criteria
- SN0014: Tightening of cobicistat degradation acceptance criteria
- SN0017: Tightening of the darunavir dissolution acceptance criterion

Our CMC group confirmed, during a recent review of documentation, that the specifications submitted with SN0017 did include the tighter cobicistat degradation criteria, along with the tighter darunavir dissolution criterion. Unfortunately, this latest set of specifications (SN0017) did not include the addition of the microbiological purity acceptance criteria submitted with SN0009. Therefore, Janssen would like to reconcile the different changes made to the specifications during review, and provide the Division with a revised set of specifications that include all of the changes made to-date as noted in each of the submissions bulleted above.

Is the Division able to accept an updated set of specifications at this time, or offer any guidance to Janssen as how best to approach the reconciliation of the various revisions made to the specifications to-date?

Should you wish to discuss further via telephone, please let me know.

Kind regards,

Karen

Karen Gerry , BSc
North American Regulatory Liaison
Janssen Research & Development LLC
Infectious Diseases



Tel: 416-382-4819

Fax: 416-449-7092

e-mail: kgerry@its.jnj.com

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NINA MANI
01/14/2015

From: Mani, Nina
To: [Gerry, Karen \[JRDCAL \(kgerry@its.jnj.com\)\]](mailto:kgerry@its.jnj.com)
Subject: NDA 205395 -- PREA PMR
Date: Monday, January 05, 2015 9:52:00 AM
Importance: High

Hi Karen:

Our team has the following revised version of PMR# 3 (12- 18 years) that they'd like your concurrence on. [REDACTED] (b) (4). The milestone timelines remain unchanged.

Previous version:

3. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir/cobicistat fixed-dose combination (FDC) tablets in HIV-infected pediatric subjects 12 years to less than 18 years of age [REDACTED] (b) (4). The safety and antiviral activity (efficacy) of darunavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 years to less than 18 years of age [REDACTED] (b) (4) may not be required if the dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products and if the FDC produces similar exposures as the individual components.

Revision:

3. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir/cobicistat fixed-dose combination (FDC) tablets in HIV-infected pediatric subjects 12 years to less than 18 years of age. The safety and antiviral activity (efficacy) of darunavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 years to less than 18 years of age may not be required if the dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products and if the FDC produces similar exposures as the individual components.

Final Protocol Submission:	03/31/2020
Study/Trial Completion:	12/31/2020
Final Report Submission:	12/31/2021

Kindly acknowledge receipt of this communication and submit your response by **Wednesday, January 7, 2015**.

Happy New Year!

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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NINA MANI
01/05/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: May 28, 2014

Application Number: 205395

Product Name: Darunavir (DRV) and Cobicistat (COBI) Fixed Dose Combination (FDC)

Sponsor/Applicant Name: Janssen Products, LP

Subject: User Fees

FDA Participants

Linda Onaga, Regulatory Project Manager

Nina Mani, Regulatory Project Manager

Karen Winestock, Chief, Project Management Staff

Sponsor/Applicant Participants

Karen Gerry, Manager, Global Regulatory Affairs

1.0 BACKGROUND:

In the December 2012 pre-NDA meeting background package for the DRV and COBI FDC, the sponsor stated that they were not seeking to establish efficacy or safety for the DRV and COBI FDC. Instead, safety and efficacy for DRV and COBI would be established under their individual NDAs. Therefore, the Applicant considers that there will not be any clinical data in the FDC NDA and thus a reduced user fee would be required. The Division was unable to provide a definitive response and requested the sponsor submit a summary of the clinical study and the redlined version of the labeling to the User Fee Staff.

On April 16, 2013, Janssen submitted the requested information to the PIND along with a request for feedback regarding their plan to submit a reduced user fee. The Division sent Janssen a communication that stated that the BE study, TMC114IFD1003 would be the pivotal study needed for approval of the DRV and COBI FDC, and based on the information provided it was determined that a reduced user fee would be assessed.

Janssen submitted the NDA in April 2014. Within the application Janssen requested 3 years of exclusivity which, they claimed, was supported by new clinical investigations that are essential for approval. The new clinical investigations included study GS –US-216-0130, a Phase 3b study evaluating DRV and COBI.

The objectives of this teleconference are to obtain clarity on the clinical trial(s) they are referring to which support their exclusivity request, and to inform them of their options with regard to evaluation of clinical data for labeling and its implications.

2.0 DISCUSSION:

Janssen interpreted the exclusivity claim to be for the DRV and COBI FDC formulation. The Division informed Janssen that only safety and efficacy evaluations from new clinical trials which are essential to approval can be used to potentially support an exclusivity claim. Therefore, the BE study, which was originally considered pivotal, did not meet the requirements set for exclusivity. However, if Janssen wants the results of Study GS-US-216-0130 in the labeling and use it to support their exclusivity claim, they are subject to the full user fee. If they decide that only the BE study, TMC114IFD1003 is essential for approval and they did not want information from Study GS-US-216-0130 in the labeling, then the user fees they have already paid would be adequate. Janssen was told that they have 5 calendar days to respond. If they decide to include study 0130 results in the labeling, the Agency expects the remaining balance of the full user fee to be submitted with their response.

If the user fee is not received within the allotted time period, Janssen was informed that an “unacceptable for filing” letter will be issued for the application and the review clock would stop.

3.0 ACTION ITEMS:

Janssen will provide the Agency with their decision within 5 calendar days of the phone call as to whether they would like the results from study 0130 in the label.

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NINA MANI
12/24/2014

From: Mani, Nina
To: "[Gerry, Karen \[JRDCA\]](#)"
Subject: RE: NDA 205395 Container Label
Date: Friday, December 19, 2014 11:13:00 AM

Hi Karen:

We have the following recommendation for the Container Label:

1. Remove [REDACTED] (b) (4) to align with DAVP's recommendation [REDACTED] (b) (4)

Please submit the revised container label to the NDA by December 23, 2014.
Kindly acknowledge receipt of this communication.

Regards,
Nina

From: Gerry, Karen [JRDCA] [mailto:kgerry@its.jnj.com]
Sent: Thursday, December 11, 2014 3:14 PM
To: Mani, Nina
Subject: RE: NDA 205395 Labeling

Hi Nina,

Janssen acknowledges receipt of the NDA 205395 FDA labeling requests of 11 December 2014.

Could FDA advise if there will be any further questions with respect to the component bottle label, as the Janssen production group would like to initiate printing of the label without having to do so by a 'risk print'?

Kind regards,

Karen

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NINA MANI
12/19/2014

From: Mani, Nina
To: "[Gerry, Karen \[JRDCA\]](#)"
Subject: RE: NDA 205395 (darunavir/cobcistat FDC) -- Clinical Pharmacology Information Request
Date: Tuesday, December 16, 2014 5:20:00 PM

Hi Karen:

We have a follow up request regarding your Clin Pharm submission of today, December 16, 2014:

For amendment 1 to the PBRL-RD-1371/TIE643EL-116433-H/BA10243 method validation report, was the darunavir long term stability data at -20C and -70C for 295 and 588 days generated using freshly prepared calibration standards?

Please provide your response to the NDA by COB, Thursday, December 18, 2014.

Kindly acknowledge receipt of this communication.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

From: Gerry, Karen [JRDCA] [mailto:kgerry@its.jnj.com]
Sent: Tuesday, December 16, 2014 10:59 AM
To: Mani, Nina
Subject: NDA 205395 (darunavir/cobcistat FDC) -- Clinical Pharmacology Response
Importance: High

Hi Nina,

Please find this email as notification that Janssen has submitted today (Seq 0021) to NDA 205395 the response to the Division's Clinical Pharmacology Information Request of 12 December 2014.

Should you have any questions in regards to the submission, please do not hesitate to contact me.

Kind regards,

Karen

Karen Gerry, BSc

**North American Regulatory Liaison
Janssen Research & Development LLC
Infectious Diseases**



Tel: 416-382-4819

Fax: 416-449-7092

e-mail: kgerry@its.jnj.com

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NINA MANI
12/16/2014

From: Mani, Nina
To: [Gerry, Karen \[JRDCAL \(kgerry@its.jnj.com\)\]](mailto:kgerry@its.jnj.com)
Subject: NDA 205395: Clinical Pharmacology Information Request
Date: Friday, December 12, 2014 8:34:00 AM

Hi Karen:

For the [REDACTED] (b) (4) darunavir method validation report, please provide the updated darunavir long term stability data [REDACTED] (b) (4) in K2EDTA plasma (and the relevant darunavir certificates of analysis) to support the reported darunavir concentration data from the GS-US-216-130 trial. In the [REDACTED] (b) (4) [REDACTED] method validation report that was submitted, only 155 days of darunavir long term stability data [REDACTED] (b) (4) in K2EDTA plasma was provided.

Please provide this information by December 16, 2014.

Kindly acknowledge receipt of this communication.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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NINA MANI
12/12/2014

Hughes, Minerva

From: Hughes, Minerva
Sent: Friday, December 05, 2014 2:23 PM
To: Hughes, Minerva
Subject: FW: Follow-up Regarding BE Inspections for NDA 205395

From: Chen, Xikui
Sent: Friday, December 05, 2014 9:50 AM
To: Scheibner, Kara; Hughes, Minerva
Cc: Mani, Nina
Subject: RE: Follow-up Regarding BE Inspections for NDA 205395

Hi Minerva,

There was no form FDA-483 issued at (b) (4) or the Belgium clinical facilities, and no significant finding. Both facilities will be classified as NAI. The review memo is pending. Thanks!

Xikui

From: Mani, Nina
To: "[Gerry, Karen \[JRDCAI\]](#)"
Subject: RE: NDA 205395 -- PREA PMRs
Date: Friday, November 21, 2014 11:02:00 AM

Hi Karen:

Based on the deferrals in the Agreed Upon PSP the Agency will be proposing the following three PMRs with associated timelines.

In particular, for **#3 (12 years to less than 18 years)**, the Division would like you to propose new dates since we believe that no new formulation development will be needed for this age group. If you want to stay with the dates currently proposed for this age cohort, please provide your justification.

1. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir/cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 3 years to less than 6 years of age and weighing at least 15 kg. The safety and antiviral activity (efficacy) of darunavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children ages 3 to less than 6 years may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age appropriate FDC produces similar exposures as the individual components.
Protocol submission: March 31, 2020
Study completion: December 31, 2020
Study submission: December 31, 2021
2. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir/cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 6 years to less than 12 years of age. The safety and antiviral activity (efficacy) of darunavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children ages 6 to less than 12 years may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age appropriate FDC produces similar exposures as the individual components.
Protocol submission: March 31, 2020
Study completion: December 31, 2020
Study submission: December 31, 2021
3. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir/cobicistat fixed-dose combination (FDC) tablets in HIV-infected pediatric subjects 12 years to less than 18 years of age [REDACTED] ^{(b) (4)}. The safety and antiviral activity (efficacy) of darunavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 years to less than 18

years of age [REDACTED] (b) (4) may not be required if the dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products.

Protocol submission: March 31, 2020
Study completion: December 31, 2020
Study submission: December 31, 2021

Kindly acknowledge receipt of this communication and provide your response by **Tuesday, November 25, 2014**. Please also submit your response to the NDA.

Regards,
Nina

From: Gerry, Karen [JRDCA] [<mailto:kgerry@its.jnj.com>]
Sent: Wednesday, October 15, 2014 2:02 PM
To: Mani, Nina
Cc: Winestock, Karen
Subject: NDA 205395 -- FDA Request of 8 October 2014 (PREA PMC)
Importance: High

Hi Nina,

As requested, Janssen is providing the appended document in regards to the requested timeline information regarding the darunavir/cobicistat formulation for pediatric patients ≥ 3 years to < 18 years of age weighing ≥ 15 kg [REDACTED] (b) (4). Should the Division have any questions in regards to the provided information, please do not hesitate to contact me.

Could you please confirm receipt of this email.

Regards,

Karen

*Karen Gerry, BSc
North American Regulatory Liaison
Janssen Research & Development LLC
Infectious Diseases*



Tel: 416-382-4819
Fax: 416-449-7092

e-mail: kgerry@its.jnj.com

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/s/

NINA MANI
11/21/2014

From: Mani, Nina
To: [Gerry, Karen \[JRDCAL \(kgerry@its.jnj.com\)\]](mailto:kgerry@its.jnj.com)
Subject: NDA 205395: Labeling and Carton and Container Label
Date: Friday, November 07, 2014 2:58:00 PM
Attachments: [NDA 205395 draft-labeling-text FDA 11 7 2014.docx](#)
[NDA 205395 draft-labeling-text FDA 11 7 2014.pdf](#)

Hi Karen:

Kindly acknowledge receipt of the attached Full Prescriber Information and Patient Information with Division comments (word and PDF) as well as, comments on the container label.

Please note that initial edits to the proposed labeling are complete.

The Division expects to make additional edits after receiving your response.

In addition we have the following general recommendation, and comments on the container label to ensure safe use of the product.

A. General Recommendation

Replace "TRADENAME" with the conditionally acceptable proprietary name, Prezcobix, where applicable throughout the labels and labeling.

B. Container Label

1. For consistency between all labels and labeling, add the statement (b) (4) to the principal display panel (PDP).

2. Remove (b) (4)

3. Move the "Alert: Find out about medicines..." statement to the principal display panel in order to more clearly display this important information. In order to accommodate this change, consider moving the "Each tablet contains..." statement to the side panel.

Please provide your response by **Monday, November 17** for carton and container label, and Labeling Text.

Thanks.

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002

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Phone: 240-402-0333

Fax: 301-796-9883

e-mail: Nina.Mani@fda.hhs.gov

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NINA MANI
11/07/2014

From: Mani, Nina
To: [Gerry, Karen \[JRDCAL \(kgerry@its.jnj.com\)\]](mailto:kgerry@its.jnj.com)
Cc: [Winestock, Karen](#)
Subject: NDA 205395 PREA PMR
Date: Wednesday, October 08, 2014 2:18:00 PM

Hi Karen:

We will be setting up a PREA PMR for NDA 205395 for darunavir/cobiscistat for pediatric patients. The team requests that you propose dates (mm/dd/yyyy) for protocol submission, study completion, and study submission for each anticipated darunavir/cobicistat formulation for pediatric patients ≥ 3 years to < 18 years of age weighing ≥ 15 kg (b) (4)

Kindly acknowledge receipt of this communication, and please get back to me and Karen Winestock (ccd) by **October 15, 2014**. Please also submit your response to the NDA.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
10/08/2014



NDA 205395

INFORMATION REQUEST

Janssen Products, LP
Attention: Karen Gerry, BSc
Manager, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Ms. Gerry:

Please refer to your New Drug Application (NDA) received March 31, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for darunavir/cobicistat tablet, 800 mg/150 mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by September 12, 2014, in order to continue our evaluation of your NDA.

BioPharmaceutics:

1. Your proposed dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in $\frac{(b)}{(4)}$ minutes for darunavir in the FDC tablet is not adequately supported by your data, and is therefore not acceptable. Based on the mean dissolution performance of the clinical and primary stability batches, an acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in 30 minutes is recommended for optimal quality control. Further, a final sampling time of 30 minutes is most sensitive to manufacturing variations and dissolution stability changes as summarized in Section 3.2.P.2 of your NDA.
2. Using the clinical batch 2CG7515-X as a reference, provide the results of similarity f1/f2 testing for each $\frac{(b)}{(4)}$ evaluated in the manufacturing DOE and development studies to support the proposed PAR for the commercial process. We note that during process development, $\frac{(b)}{(4)}$
 $\frac{(b)}{(4)}$
An f2 value of $\leq \frac{(b)}{(4)}$ suggests an inappropriate boundary for a PAR.

CMC:

For darunavir drug substance, we have the following recommendations:

1. Add manufacturers' information for darunavir drug substance in 3.2.S.2.1, as you did for cobicistat drug substance.

2.  (b) (4)

For the drug product, we have the following recommendations:

1.  (b) (4)
2. For acceptance criteria of some of your specified degradants of cobicistat for shelf life/stability studies, we recommend the following revision:

Degradant Code	NDA proposed limit (%) at shelf life	FDA proposed limit (%) at shelf life
 (b) (4)	 (b) (4)	 (b) (4)

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

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

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/s/

STEPHEN MILLER
08/27/2014
For R.Madurawe

From: [Gerry Karen \[JRDC\]](#)
To: [Mani Nina](#)
Subject: RE: NDA 205395 Pediatric Certification
Date: Thursday, August 07, 2014 11:52:21 AM
Attachments: [emfinfo.txt](#)

Hi Nina,

Janssen will review NDA 202022 (SEQ 0004) and the associated 'Signature page', and will provide for NDA 205395.

Regards,

Karen

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: August-07-14 10:38 AM
To: Gerry, Karen [JRDC]
Cc: Winestock, Karen
Subject: RE: NDA 205395 Pediatric Certification

Hi Karen:

Please refer to NDA 202022, rilpivirine and the certification provided on 9/24/2010 Sequence # 0004, 1.9.2 with the "Request for Pediatric Deferral- Signature Page".
Kindly provide similar certifications for the pediatric deferrals and waivers being sought for the DRV/COBI FDC.

Regards,
Nina

From: Mani, Nina
Sent: Monday, July 28, 2014 2:22 PM
To: 'Gerry, Karen [JRDC]'
Cc: Winestock, Karen
Subject: RE: NDA 205395 Pediatric Certification

Hi Karen:

Please note that whenever an application triggers PREA and you submit the Agreed iPSP, you are still required to submit waiver and/deferral requests and certification with your NDA submission. Please see the Guidance –"How to comply with the Pediatric Research Equity Act (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf>) for more information. The waiver and deferral requests (including certifications) will be reviewed by the Pediatric Review Committee.

Regards,
Nina

From: Gerry, Karen [JRDC] [mailto:kgerry@its.jnj.com]
Sent: Sunday, July 27, 2014 3:03 PM
To: Mani, Nina
Subject: RE: NDA 205395
Importance: High

Hi Nina,

Janssen included in the NDA (b) (4) submission (Module 1.9.4) an agreed upon 'Initial Pediatric Study Plan' (iPSP) based on the new PSP Guidance of July 2013. Janssen received confirmation of agreement from the Division on 21 March 2013 (appended email correspondence from L. Onaga) whereby the Division stated that

“...we confirm our agreement to your Agreed iPSP to study darunavir/cobicistat fixed dose combination in pediatric patients 3 to less than 18 years of age with HIV-1 infection. We have completed our review of the submission, and we confirm our agreement to your Agreed iPSP. We have no further comments on your PSP.”, and that the agreed iPSPs should be included in the Janssen New Drug Application.

Janssen was not aware that there was any further documentation needed in the submission in regards to pediatric waivers and deferrals in the study of the darunavir/cobicistat fixed dose combination in pediatric patients 3 to less than 18 years of age with HIV-1 infection.

Could FDA please advise.

Regards,

Karen

Karen Gerry, BSc
North American Regulatory Liaison
Janssen Research & Development LLC
Infectious Diseases



Tel: 416-382-4819

Fax: 416-449-7092

e-mail: kgerry@its.jnj.com

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From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: July-25-14 4:45 PM
To: Gerry, Karen [JRDCA]
Subject: NDA 205395

Hi Karen:

During our review of your submission, we note that you have submitted a request for pediatric waivers and deferral.

However, we could not locate the certification that is required under 21, CFR 314.55. If you have submitted this information, please provide the location.

If not, please submit this information no later than August 4, 2014.

Regards,
Nina

Nina Mani, Ph.D., MPH

Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
08/07/2014

From: Mani, Nina
To: [Gerry, Karen \[JRDCAL \(kgerry@its.jnj.com\)\]](mailto:kgerry@its.jnj.com)
Subject: NDA 205395
Date: Monday, August 04, 2014 4:38:00 PM

Hi Karen;

The Clinical team requests the following to aid in the ongoing review of your submission:

In our analysis of Study GS-US-216-0130, we are unable to reproduce the serum glucose abnormalities (hyperglycemia and hypoglycemia) listed in Table 5.5.1. Please provide guidance on how the glucose values in this table were created, including all the variables used.

Kindly acknowledge receipt of this communication and provide your response by **Monday, August 18, 2014**.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
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/s/

NINA MANI
08/04/2014

MEMORANDUM



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

DATE: 16 July 2014

TO: NDA 205395

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPS/NDMS

THROUGH: John Metcalfe, Ph.D.
Senior Review Microbiologist
CDER/OPS/NDMS

cc: Nina Mani
Regulatory Health Project Manager
CDER/OND/OAP/DAVP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Darunavir/Cobicistat [Submission Date: 31 March 2014]

The NDA for Darunavir/Cobicistat proposes a waiver of microbial limits testing for drug product release. The applicant provides a suitable rationale for the exclusion of this testing, and microbial limits testing will be performed as a part of the stability program. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

The proposed drug product containing Darunavir and Cobicistat is a ^{(b) (4)} film-coated tablet for oral administration. ^{(b) (4)}

The applicant presents a rationale for waiving microbial enumeration testing for product release. ^{(b) (4)}

The applicant provides stability data to demonstrate a lack of microbial growth in the finished product. Microbial enumeration testing was performed for three primary stability batches

MEMORANDUM

(2CG7514-X, 2CG7515-X, and 2CG7516-X). Product was held at (b) (4), and (b) (4). Microbiological specifications for these studies are in agreement with those described in USP <1111>, and include a total aerobic microbial count of NMT (b) (4)

Microbiological stability data provided met acceptance criteria. Testing was performed using methods described in USP <61> and USP <62>. A description of method verification studies was provided in the application. The drug product will be tested for microbial enumeration and the absence of *E. coli* annually as part of the stability program.

ADEQUATE

Reviewer Comments – The applicant’s proposal to waive microbial limits testing for product release is acceptable.

END

Filing Review Information Request

1. *You state that microbiological purity of your drug product is ensured by the use of a validated manufacturing process, but you do not provide information detailing the validation process or the steps taken in manufacturing to ensure microbiological quality. Describe these steps and their associated validation studies.*
2. *It is unclear if you plan to perform microbial enumeration testing as part of your stability program. Please note that you should perform microbial enumeration testing minimally at the initial testing time point. Clarify the stability testing schedule for microbial enumeration testing.*
3. *Provide a statement verifying that microbial enumeration testing methods are suitable for use with the drug product.*

14 July 2014 Response

The applicant provided the requested information, including a revised stability specification. The information is reviewed in the preceding section.

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/s/

ERIKA A PFEILER
07/16/2014

JOHN W METCALFE
07/16/2014
I concur.

From: Mani, Nina
To: "[Gerry, Karen \[JRDCA\]](#)"
Subject: RE: NDA 205395 IR
Date: Tuesday, July 15, 2014 2:02:00 PM

Hi Karen:

Please submit your response by August 11, 2014. Also, if this results in revisions to the label please submit it at the same time.

Thanks,
Nina

From: Gerry, Karen [JRDCA] [mailto:kgerry@its.jnj.com]
Sent: Tuesday, July 15, 2014 1:31 PM
To: Mani, Nina
Subject: RE: NDA 205395 IR

Hi Nina,

Janssen acknowledges receipt of the below communication. Could you advise as to the timeline for response to FDA?

Regards,

Karen

Karen Gerry , BSc
North American Regulatory Liaison
Janssen Research & Development LLC
Infectious Diseases



Tel: 416-382-4819
Fax: 416-449-7092
e-mail: kgerry@its.jnj.com

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From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: July-15-14 1:19 PM
To: Gerry, Karen [JRDCa]
Subject: NDA 205395 IR

Hi Karen:

In the label submitted as part of the NDA currently under review, the Clinical Virology team has the following comment and request regarding Section 12: Clinical Pharmacology, Sub-section: 12.4 Microbiology, Sub-subsection: *Cross-resistance*.

In the label it states that ‘.....*Darunavir has a less than 10 fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to these PIs remain susceptible to darunavir*’. Please identify any of these protease inhibitors for which the percentage of isolates was much less than 90% and provide the supporting data for all. PIs that fall significantly below 90% should be identified in your labels.

Kindly acknowledge receipt of this communication.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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INDs not in eCTD format).

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/s/

NINA MANI
07/15/2014

From: Mani, Nina
To: "Nair, Nancy [JRDUS]"
Subject: RE: NDA 205-123/S-002
Date: Wednesday, June 04, 2014 12:32:00 PM

Yes, that is fine.

Thanks.

From: Nair, Nancy [JRDUS] [mailto:NNair@its.jnj.com]
Sent: Wednesday, June 04, 2014 12:31 PM
To: Mani, Nina
Subject: RE: NDA 205-123/S-002

Hi Nina

Thanks for the guidance. 2 months from the COSMOS Submission (May 6, 2014) would be July 6, 2014. Since it falls on a Sunday, would DAVP agree to us submitting it by the next business day, Monday, July 7?

Thanks
Nancy

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Wednesday, June 04, 2014 12:07 PM
To: Nair, Nancy [JRDUS]
Subject: RE: NDA 205-123/S-002

Hi Nancy:

Our clinical team requests that you submit a 2 month safety update, including a summary of the postmarketing safety experience with the combination regimen.
Kindly acknowledge receipt of this communication.

Regards,
Nina

From: Nair, Nancy [JRDUS] [mailto:NNair@its.jnj.com]
Sent: Tuesday, June 03, 2014 12:45 PM
To: Mani, Nina
Subject: NDA 205-123/S-002

Hi Nina

In reference to NDA 205-123/S-002, the COSMOS submission, Janssen would like to confirm that we would not be required to submit a 2 or 4 month safety update report for the referenced sNDA. Janssen intends on providing safety information from all the ongoing studies in the upcoming PBRR (reporting period Nov 22-2013- May 21,2014) and the PADER (reporting period May 22-

2014-August 21, 2014). Kindly confirm if this is acceptable with the Division or provide further guidance.

Thanks very much and I look forward to your response,
Nancy

Nancy V. Nair, PharmD, MBA
Associate Director, Global Regulatory Affairs
Janssen Research & Development, LLC
920 Route 202 South
Raritan NJ 08869
Office: (908) 927-3779
Fax: (908) 704-1501



IND 113198
NDA 205395

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Janssen Products, LP
1125 Trenton-Harbourton Road
Titusville, NJ 08560

ATTENTION: Karen Gerry, B.Sc.
Manager, Global Regulatory Affairs

Dear Ms. Gerry:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and your New Drug Application (NDA) dated and received March 31, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Darunavir/Cobicistat Tablets, 800mg/150 mg.

We also refer to:

- Your correspondence to your IND, dated and received January 14, 2014, requesting review of your proposed proprietary name, Prezcobix
- Your correspondence to your NDA, dated and received March 31, 2014, requesting review of your proposed proprietary name, Prezcobix

We have completed our review of the proposed proprietary name Prezcobix, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your March 31, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Nina Mani, at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
05/27/2014

TODD D BRIDGES on behalf of KELLIE A TAYLOR
05/27/2014

From: Mani, Nina
To: Gerry, Karen [JRDCAI] (kgerry@its.jni.com)
Subject: NDA 205395
Date: Monday, April 28, 2014 4:46:00 PM

Hi Karen:

Our review team has the following request for this NDA:

Please submit the contact information (e-mail, telephone and fax numbers) for the clinical and analytical facilities/sites associated with Study TMC 1141FD1003 titled "A single-dose, open-label, 3-panel, randomized, pivotal crossover study to assess the bioequivalence of darunavir when coadministered with cobicistat as either a fixed dose combination tablet (G006) or as single agents under fed and fasted conditions in healthy subjects" to the NDA.

Kindly acknowledge receipt of this communication.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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NDA 205395

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Janssen Products, LP
1125 Trenton-Harbourton Road
Titusville, NJ 08560

ATTENTION: Karen Gerry, B.Sc.
Manager, Global Regulatory Affairs

Dear Ms. Gerry:

Please refer to your New Drug Application (NDA) dated and received March 31, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Darunavir/Cobicistat, Tablets, Darunavir 800 mg/Cobicistat 150 mg.

We also refer to your correspondence dated and received March 31, 2014, requesting a review of your proposed proprietary name, Prezco**ix**. Upon preliminary review of your submission, we have determined that it is a complete submission as described in our Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*.

Therefore, the user fee goal date is June 29, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact Nina Mani, Regulatory Project Manager in the Office of New Drugs, at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Danyal Chaudhry, M.P.H.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
04/04/2014



NDA 205395

NDA ACKNOWLEDGMENT

Janssen Products, LP
Attention: Karen Gerry, BSc
Manager, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Ms. Gerry:

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

Name of Drug Product: darunavir/cobicistat, tablet (800 mg/150 mg)

Date of Application: March 31, 2014

Date of Receipt: March 31, 2014

Our Reference Number: NDA 205395

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2014, in accordance with 21 CFR 314.101(a).

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

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

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

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

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If you have any questions, call me at (240) 402-0333 or the Division's number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Nina Mani, PhD, MPH
Regulatory Project Manger
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

NINA MANI
04/03/2014