

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206353Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206353

SUPPL #

HFD #

Trade Name EVOTAZ

Generic Name atazanavir ^{(b) (4)} and cobicistat

Applicant Name Bristol-Myers Squibb Company

Approval Date, If Known February 4, 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.

This NDA package includes clinical data from one Phase 1 study (AI424511 – “A Randomized, 5-Period, Crossover Study in Healthy Subjects to Assess the Bioequivalence of Atazanavir when Co-Administered with Cobicistat as a Fixed Dose Combination Relative to the Single Agents Following a Light Meal, the Relative Bioavailability of Atazanavir when Co-Administered with Cobicistat as a Fixed Dose Combination Relative to the Single Agents Under Fasted Conditions, and the Effect of Food on the Bioavailability of Atazanavir in the Fixed Dose Combination”).

The bioequivalence (BE)/bioavailability (BA) trial AI424511 is pivotal for approval of this application of ATV/COBI (ATV/co) 300/150 mg as a FDC tablet indicated in combination with other antiretroviral agents for treatment of HIV-1 infection in adults.

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:

N/A

d) Did the applicant request exclusivity?

YES NO

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

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# 21567 atazanavir

NDA# 206352 atazanavir

NDA# 203094 cobicistat

NDA# 203100 elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree

with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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	!
IND #	!
YES <input type="checkbox"/>	! NO <input type="checkbox"/>
	! Explain:

Name of person completing form: Sammie Beam, RPh
Title: Regulatory Project Manager
Date: January 5, 2015

Name of Office/Division Director signing form: Jeffrey Murray
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/

SAMMIE G BEAM
01/09/2015

JEFFREY S MURRAY
01/09/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206353 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: EVOTAZ Established/Proper Name: atazanavir and cobicistat Dosage Form: FDC		Applicant: Bristol-Myers Squibb Company Agent for Applicant (if applicable):
RPM: Sammie Beam		Division: Division of Antivirals
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)	<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <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) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>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.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>2/4/14</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): 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 checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ 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 <i>(including approval letter with final labeling)</i>	Approval January 29, 2015
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 <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included 1/28/15
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 4/4/14
❖ 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 type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included 1/28/15
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 4/4/14
❖ 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 	<input checked="" type="checkbox"/> Included 1/22/15
❖ 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> 	Acceptable Letter 6/8/14 Review 6/4/14
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: PLR Format Review 6/6/14 DMEPA: 1/6/15; 11/18/14 DMPP/PLT and OPDP 1/9/15 OPDP: 1/12/15 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 <i>(indicate date of each review)</i>	Filing Review 7/9/14
❖ 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 <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ 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

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>12/17/14</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>)	1/27/15;1/23/15; 1/21/15; 1/15/15; 1/9/15 (2); 12/22/14; 12/17/14; 12/3/14; 12/1/14; 11/25/14; 11/19/14; 8/27/14; 6/12/14; 6/10/14; 6/6/14; 4/17/14; 4/10/14
❖ 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>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg 12/9/13 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
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>)	1/14/15
PMR/PMC Development Templates (<i>indicate total number</i>)	4
Clinical	
❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 12/22/14 <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>)	12/22/14 in Appendix (pg 5) of Clinical Review
❖ 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"/> 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>)	1/5/15, 12/30/14
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" 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>)	12/29/14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	7/14/14
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	12/24/14
❖ 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>	Product Quality Review 12/18/14 Biopharmaceutics Review 12/15/14
❖ Microbiology Reviews	
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	5/16/14
<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 checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	12/18/14 (pg 69 of Product Quality Review)
<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 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: 9/17/14 <input checked="" type="checkbox"/> Acceptable <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 checked="" 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 checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

SAMMIE G BEAM
01/30/2015

ELIZABETH G THOMPSON
01/30/2015

From: [Beam, Sammie](#)
To: [Percival, Lisa \(Lisa.Percival@bms.com\)](mailto:Lisa.Percival@bms.com)
Subject: NDA 206353 revised labeling
Date: Tuesday, January 27, 2015 12:53:17 PM
Attachments: [206353 Labeling1.27.15.docx](#)

Hi Lisa,

We found one previous revision not changed and there is another revision.

Please respond back by tomorrow with revised labeling or your response if don't agree.

I made changes in the year on the document already.

****Please acknowledge receipt****

Kind regards,

Sammie

Sammie Beam, RPh.

CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

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/s/

SAMMIE G BEAM
01/27/2015

From: [Beam, Sammie](#)
To: [Percival, Lisa \(Lisa.Percival@bms.com\)](mailto:Lisa.Percival@bms.com)
Bcc: [Beam, Sammie](#)
Subject: NDA 206353 Proposed revision to labeling
Date: Friday, January 23, 2015 9:14:39 AM
Attachments: [bms21jan-initnda-ataza-cobic-pro LC.doc](#)

Hello Lisa,

Please see the attached for the addition of a contraindication.

Kind regards,

Sammie

Sammie Beam, RPh.

CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

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SAMMIE G BEAM
01/23/2015

From: [Beam, Sammie](#)
To: ["Percival, Lisa"](#)
Subject: RE: ATV/COBI PPI questions
Date: Wednesday, January 21, 2015 10:31:16 AM

Hello Lisa,

Please see our response below each comment/question.

Kind regards,
Sammie

****Please acknowledge receipt of this email****

Sammie Beam, RPh.
CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, January 16, 2015 4:05 PM
To: Beam, Sammie
Subject: ATV/COBI PPI questions

Hi Sammie,

After review, Reyataz and Evotaz are still included (for Reyataz, please see page 1 'What is Evotaz?' In FDA document sent 1/15/15 and for Evotaz please see page 1 'under PI heading and page 2 under 'Do not take Evotaz if...' And throughout). Therefore, we propose the language should read:

"REYATAZ and EVOTAZ are trademarks of Bristol-Myers Squibb Company. Other brands listed are the trademarks of their respective owners and are not trademarks of Bristol-Myers Squibb Company."

FDA Response: This language is acceptable.

In addition, upon proof reading the draft sent to you earlier we found two additional changes we think are necessary:

1. In FDA PPI document (page 2), Mitigare was listed with (b) (4)
[REDACTED] Since Mitigare is colchicine we believe it should be moved there. Also Mitigare is a

(b) (4)

so we propose the super scripted 'TM' instead.

FDA Response: We agree with your proposal.

(b) (4)

Please advise on how to proceed with the issues above or let me know if you need to discuss.

Thanks and kind regards,
Lisa

Sent from my iPhone

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/s/

SAMMIE G BEAM
01/21/2015

From: [Beam, Sammie](#)
To: [Percival, Lisa \(Lisa.Percival@bms.com\)](#)
Subject: NDA 206353 revised labeling and label comments
Date: Thursday, January 15, 2015 1:54:55 PM
Attachments: [206353 Labeling PI 1.15.15.docx](#)
[NDA 206353 Evotaz PPI DMPP marked copy.docx](#)

Hello Lisa,

Please see the latest proposed revisions on the PI and Patient Labeling. Our changes were made on top of your tracked changes version. I was not able to accept some of the additions in the text so you will need to accept both your changes we agreed to, as well as any changes we made. I apologize if that adds more work for you.

The Patient Labeling is separate and should have only our tracked changes.

For the carton/container label I want to remind you to remove the (b) (4)

Also, please add "Take with food" to the label.

Let me know if you have any questions.

Kind regards,

Sammie

Sammie Beam, RPh.

CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

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/s/

SAMMIE G BEAM
01/15/2015

From: [Percival, Lisa](#)
To: [Beam, Sammie](#)
Subject: RE: NDA 206353 Proposed PREA PMRs
Date: Friday, January 09, 2015 2:02:17 PM

Thanks for all of your efforts in clarifying the process, Sammie. We accept these PREA commitments.

Thanks again,
Lisa

From: Beam, Sammie [mailto:Sammie.Beam@fda.hhs.gov]
Sent: Friday, January 09, 2015 1:09 PM
To: Percival, Lisa
Subject: RE: NDA 206353 Proposed PREA PMRs

Hello Lisa,

As we discussed on the phone, re: #2 below--if needed, a deferral request would need to come in 90 days before the Final Report Submission if the BE fails, so the timelines can be deferred to allow for a clinical trial.

Kind regards,
Sammie

Sammie Beam, RPh.
CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Friday, January 09, 2015 12:02 PM
To: Beam, Sammie
Subject: RE: NDA 206353 Proposed PREA PMRs

Hi Sammie,

Thanks again for our previous conversations regarding clarifications on these commitments. As we discussed:

1. submission of the BE study protocol, completion of the BE protocol and submission of the BE report on the timelines noted in these PMRs will allow for us to be considered on track with our PREA commitments
2. a deferral extension request for these commitments would not be required to be submitted until after completion of the BE study (i.e., after 2/2019) and not 90 days before any of the due dates in your email.

I believe the above is what we discussed, so if you agree please let me know and

then I will confirm our agreement.
Thanks so much and kind regards,
Lisa

From: Beam, Sammie [<mailto:Sammie.Beam@fda.hhs.gov>]
Sent: Friday, January 09, 2015 11:56 AM
To: Percival, Lisa
Subject: FW: NDA 206353 Proposed PREA PMRs

Hello Lisa,

This is our latest proposed PMR wording and timelines for NDA 206353. We acknowledge that the timelines below are for the BE studies and should you need to do clinical studies, FDASIA allows you to request a deferral extension with your reasons for the delay.

- 1 Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 3 months to less than 3 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 3 months to less than 3 years of age 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.

Final Protocol Submission: 03/2018
Study/Trial Completion: 08/2018
Final Report Submission: 02/2019

- 2 Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 3 years to less than 6 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 3 years to less than 6 years of age 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.

Final Protocol Submission: 03/2018
Study/Trial Completion: 08/2018

Final Report Submission: 02/2019

- 3 Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/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 atazanavir/cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 6 years to less than 12 years of age 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.

Final Protocol Submission: 03/2018

Study/Trial Completion: 08/2018

Final Report Submission: 02/2019

- 4 Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 12 years to less than 18 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC age-appropriate formulation 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 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.

Final Protocol Submission: 03/2018

Study/Trial Completion: 08/2018

Final Report Submission: 02/2019

Please acknowledge receipt and let me know as soon as possible if these are acceptable.

Kind regards,
Sammie

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/s/

SAMMIE G BEAM
01/09/2015

From: [Beam, Sammie](#)
To: [Percival, Lisa \(Lisa.Percival@bms.com\)](mailto:Lisa.Percival@bms.com)
Subject: FW: NDA 206353 Proposed PREA PMRs
Date: Friday, January 09, 2015 11:55:40 AM

Hello Lisa,

This is our latest proposed PMR wording and timelines for NDA 206353. We acknowledge that the timelines below are for the BE studies and should you need to do clinical studies, FDASIA allows you to request a deferral extension with your reasons for the delay.

- 1 Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 3 months to less than 3 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 3 months to less than 3 years of age 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.

Final Protocol Submission: 03/2018
Study/Trial Completion: 08/2018
Final Report Submission: 02/2019

- 2 Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 3 years to less than 6 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 3 years to less than 6 years of age 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.

Final Protocol Submission: 03/2018
Study/Trial Completion: 08/2018
Final Report Submission: 02/2019

- 3 Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/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 atazanavir/cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 6 years to less than 12 years of age 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.

similar exposures as the individual components.

Final Protocol Submission: 03/2018
Study/Trial Completion: 08/2018
Final Report Submission: 02/2019

- 4 Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 12 years to less than 18 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC age-appropriate formulation 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 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.

Final Protocol Submission: 03/2018
Study/Trial Completion: 08/2018
Final Report Submission: 02/2019

Please acknowledge receipt and let me know as soon as possible if these are acceptable.

Kind regards,
Sammie

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/s/

SAMMIE G BEAM
01/09/2015

From: [Beam, Sammie](#)
To: [Percival, Lisa \(Lisa.Percival@bms.com\)](mailto:Lisa.Percival@bms.com)
Subject: 206353 Proposed Labeling 12.22.14
Date: Monday, December 22, 2014 7:42:06 AM
Attachments: [206353 Labeling12.22.14.docx](#)
Importance: High

Hi Lisa,

Please see tracked changes and comments in the attached word version of the labeling for our proposals. If possible, can you review and return your response to us by December 31, 2014.

Kind regards,

Sammie

Sammie Beam, RPh.

CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

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SAMMIE G BEAM
12/22/2014

From: [Beam, Sammie](#)
To: [Percival, Lisa \(Lisa.Percival@bms.com\)](mailto:Lisa.Percival@bms.com)
Subject: NDA 206353 Proposed PREA PMRs
Date: Wednesday, December 17, 2014 2:46:20 PM

Hi Lisa,

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

1. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) tablets in HIV-infected pediatric subjects 3 years to less than 6 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 3 years to less than 6 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 age appropriate FDC produces similar exposures as the individual components.

Final Protocol Submission: 03/31/2018
Study/Trial Completion: 08/31/2018
Final Report Submission: 02/28/2019

2. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) tablets in HIV-infected pediatric subjects 3 months to less than 3 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 3 months to less than 3 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 age appropriate FDC produces similar exposures as the individual components.

Final Protocol Submission: 03/31/2018
Study/Trial Completion: 08/31/2018
Final Report Submission: 02/28/2019

3. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/cobicistat fixed-dose combination (FDC) tablets in HIV-infected pediatric subjects 6 years to less than 12 years of age. The safety and antiviral activity (efficacy) of atazanavir/cobicistat FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 6 years to less than 12 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 age appropriate FDC produces similar exposures as the individual components.

Final Protocol Submission: 03/31/2018
Study/Trial Completion: 08/31/2018
Final Report Submission: 02/28/2019

4. Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of atazanavir/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 atazanavir/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 age appropriate FDC produces similar exposures as the individual components.

Final Protocol Submission: 03/31/2018
Study/Trial Completion: 08/31/2018
Final Report Submission: 02/28/2019

Please acknowledge receipt of this communication and provide your as soon as reasonable, but at the latest by Monday, December 29, 2014. Please also submit your response to the NDA.

Kind regards,

Sammie

Sammie Beam, RPh.

CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

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SAMMIE G BEAM
12/17/2014

From: [Beam, Sammie](#)
To: "Percival, Lisa"
Subject: RE: NDA 206353 revised labeling and label comments
Date: Wednesday, December 03, 2014 11:14:30 AM

Hello Lisa,

Please see the response from the team below:

Please alphabetize drug classes (with the exception of antivirals, which should be listed first) within Table 5 to enhance readability. Note that the Division's edits (formatting, drug classes and subclasses, etc.) were intended to align Table 5 with the relevant table in the Tybost prescribing information as the latter has been updated more recently (b) (4)

Kind regards,
Sammie

Sammie Beam, RPh.
CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

From: Percival, Lisa [mailto:Lisa.Percival@bms.com]
Sent: Monday, December 01, 2014 3:06 PM
To: Beam, Sammie
Subject: RE: NDA 206353 revised labeling and label comments

Hi Sammie,

Quick format question. For table 5, FDA commented (A18) to standardize drug class headings and subheadings and list drug classes in alphabetical order. (b) (4)

[Redacted]

We are having a meeting to discuss tonight and tomorrow morning, so if there are any other questions I'll send all at once tomorrow. This was the first question that came up from our labeling operations today.

Thanks again,
Lisa

From: Beam, Sammie [mailto:Sammie.Beam@fda.hhs.gov]
Sent: Monday, December 01, 2014 11:43 AM

To: Percival, Lisa
Subject: NDA 206353 revised labeling and label comments

Hi Lisa,

Please see above for proposed changes. I have attached a word document for the labeling.

Kind regards,
Sammie

Sammie Beam, RPh.
CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

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/s/

SAMMIE G BEAM
12/03/2014



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: December 1, 2014
To: Lisa Percival, Director, Global Regulatory Strategy
From: Sammie Beam, RPh, Regulatory Project Manager
Sponsor: Bristol-Myers Squibb Company
NDA: 206353
Drug: EVOTAZ (atazanavir and cobicistat)
Subject: Proposed Labeling and Label revisions

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the treatment of HIV infection. Please see our comments below for the carton/container labels and our attached proposed labeling revisions. Please submit new revised labeling and labels by December 10, 2014.

Container and Carton Labels:

1. Change the following statement.



To: "Each tablet contains 342 mg of atazanavir sulfate, equivalent to 300 mg of atazanavir, and 150mg cobicistat."

2. As previously agreed change the name to: EVOTAZ (atazanavir and cobicistat) tablets; 300mg / 150 mg

PLEASE REPLY BY EMAIL (sammie.beam@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0080). We are providing the above information via electronic mail for your convenience.

Sammie Beam, RPh.
CAPT, U.S. Public Health Service
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

Attachment: proposed labeling changes

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/s/

SAMMIE G BEAM
12/01/2014

From: [Beam, Sammie](#)
To: [Percival, Lisa \(Lisa.Percival@bms.com\)](mailto:Lisa.Percival@bms.com)
Subject: NDA 206353 Proposed Timelines Pediatric Studies IR
Date: Tuesday, November 25, 2014 2:35:08 PM

Hello Lisa,

Can you provide the proposed dates (below) for each submission to the FDA for pediatric studies. I realize that some of the information is included in the submission, but I want it to be organized together. If more than one, list it separately for each.

- a. Protocol Submission:**
- b. Study Completion:**
- c. Study Submission:**

If you can, please provide a response by e-mail by COB tomorrow, and also submit to the application.

Kind regards,

Sammie

Sammie Beam, RPh.

CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Bldg 22 Room 6317
10903 New Hampshire
Silver Spring, Maryland 20993
301-796-0080

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/s/

SAMMIE G BEAM
11/25/2014

Cuff, Althea

From: Cuff, Althea
Sent: Wednesday, November 19, 2014 3:30 PM
To: Percival, Lisa (Lisa.Percival@bms.com)
Cc: Beam, Sammie
Subject: NDA 206353 - Information Request

Dear Ms. Percival:

Based on the dissolution performance of your clinical batch, development, and registration lots, with consideration of the likely process ranges at commercial scale, we do not consider your proposed ATV acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes optimal for product quality control. We recommend an acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 30 minutes for ATV. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing.

Provide a revised drug product specification table reflecting this change with a commitment to amended protocols, as needed, before utilization.

A response is requested by COB Tuesday, 25 November 2014.

Thanks, Althea

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/s/

ALTHEA CUFF
11/19/2014



NDA 206353

INFORMATION REQUEST

Bristol-Myers Squibb Company
Attention: Lisa Percival
Director, Global Regulatory Strategy
5 Research Parkway, Mailstop 2CW-506
Wallingford, CT 06492

Dear Ms. Percival:

Please refer to your New Drug Application (NDA) dated and received April 4, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for EVOTAZ (atazanavir (b) (4)/cobicistat) fixed dose combination tablet, 300mg/150mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by September 19, 2014, in order to continue our evaluation of your (b) (4).

- 1) Please refer to your NDA 206-353, in particular the four newly discovered cobicistat degradants, (b) (4) (3.2.P.5.5). Based on the structures, and the likely mechanism of formation, we believe it is possible that these may also form as degradants in the cobicistat on silicon dioxide drug substance. Please indicate whether any of these degradants have been detected in cobicistat on silicon dioxide drug substance, by your own analysis, or reported in Certificates of Analysis. We recommend you contact the supplier of cobicistat drug substance (Gilead) to insure that suitable analytical methods are being used at all stages.
- 2) We request that you consider voluntarily modifying (b) (4) this product by omitting the (b) (4) for the atazanavir component. Since your product has the strength of atazanavir expressed as the free base, this approach would support the adoption by USP of future drug product monographs (b) (4)

For

reference, see the Cumulative List of Nomenclature Decisions (August 2010 to February 2014) on <http://www.usp.org/usp-nf/development-process/compendial-nomenclature>

FDA supports the approach that USP is taking, as it leads to monographs where the title and strength match. Please refer to the Dec 2013 draft guidance on Naming of Drug Products Containing Salt Drug Substances (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf>).

We recommend that you change the name of this product to:

EvoTaz (atazanavir and cobicistat) tablets; 300mg / 150 mg

The container labels and the prescribing information should continue to include a statement such as (b) (4)

Please make this change in the container labels and at appropriate places in the prescribing information, and submit amended labels and labeling.

Submit revised content of labeling 21 CFR 201.100(d)(3) in structured product labeling (SPL) format as described at: <http://www.fda.gov/oc/datacouncil/spl.html>.

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



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: June 12, 2014
To: Lisa Percival, Director, Global Regulatory Strategy
From: Sammie Beam, RPh, Regulatory Project Manager
Sponsor: Bristol-Myers Squibb Company
NDA: 206353
Drug: EVOTAZ (atazanavir/cobicistat)
Subject: Information Request

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the treatment of HIV infection

We request that you submit the following information:

1. We notice from the 356h form that the following sites are involved in the manufacturing and testing of cobicistat on silicon dioxide:

[Redacted] (b) (4)

Please confirm that these are the ONLY sites used for the manufacture and testing of cobicistat on silicon dioxide and that material manufactured or tested at other sites will not be used under this NDA.

2. Please provide a Letter of Authorization to refer to NDA 21-567 for Reyataz Capsules in connection with this NDA.
3. Include in Module 3 the current information on atazanavir sulfate and cobicistat on silicon dioxide drug substances (such as manufacturers, physico-chemical properties, specifications, storage conditions and retest dates, etc.), as well as a discussion of attributes of atazanavir sulfate and cobicistat on silicon dioxide drug substances that are important for the manufacture and quality of the atazanavir and cobicistat tablets.
4. Please confirm that the (b) (4) studies described in 3.2.P.3.3.2 apply to the (b) (4) atazanavir and cobicistat (b) (4) as described in the batch formula in

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

PLEASE REPLY BY EMAIL (sammie.beam@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0080). We are providing the above information via electronic mail for your convenience.

Sammie Beam, RPh.
CAPT, U.S. Public Health Service
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SAMMIE G BEAM
06/12/2014



NDA 206353

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Bristol-Myers Squibb Company
Attention: Lisa Percival
Director, Global Regulatory Strategy
5 Research Parkway, Mailstop 2CW-506
Wallingford, CT 06492

Dear Ms. Percival:

Please refer to your New Drug Application (NDA) dated and received April 4, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for EVOTAZ (atazanavir (b) (4)/cobicistat) fixed dose combination tablet, 300mg/150mg.

We also refer to your amendments dated April 24, 2014, April 28, 2014 and June 10, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is February 4, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 7, 2015.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

GENERAL COMMENT

1. Please incorporate any labeling changes that were approved on June 2, 2014 for REYATAZ (atazanavir) that would be appropriate for this fixed-dose combination of atazanavir/cobicistat.

HIGHLIGHTS

2. There is less than ½ inch margin between the columns.
3. The HL length is greater than one-half page.

FULL PRESCRIBING INFORMATION

4. There is inconsistency of the presentation for the cross-references. Please use this example as a correct presentation “[*see Warnings and Precautions (5.3)*].”

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 1, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We also acknowledge that we granted a waiver for REYATAZ (atazanavir) capsules (NDA 21567 S-015) on March 25, 2008 and this application contains information for both atazanavir and cobicistat. We will consider your request during labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

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

If you have any questions, call Sammie Beam, Regulatory Project Manager, at (301) 796-0080.

Sincerely,

{See appended electronic signature page}

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

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/s/

JEFFREY S MURRAY
06/10/2014



NDA 206353

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb Company
5 Research Parkway, Mailstop 2CW-506
Wallingford, CT 06492

ATTENTION: Lisa Percival
Director, Global Regulatory Strategy

Dear Ms. Percival:

Please refer to your New Drug Application (NDA) dated and received April 4, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atazanavir/Cobicistat Tablets, 300 mg/150 mg.

We also refer to your correspondence, dated and received April 4, 2014, requesting review of your proposed proprietary name, Evotaz. We have completed our review of the proposed proprietary name Evotaz, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your April 4, 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 Sammie Beam, at (301) 796-0080.

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
06/06/2014

KELLIE A TAYLOR
06/08/2014



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: June 6, 2014
To: Lisa Percival, Director, Global Regulatory Strategy
From: Sammie Beam, RPh, Regulatory Project Manager
Sponsor: Bristol-Myers Squibb Company
NDA: 206353
Drug: EVOTAZ (atazanavir/cobicistat)
Subject: Information Request

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the treatment of HIV infection. Please see our following request:

Please submit the validation report for the bioanalytical methods used in study AI424511 (Report [REDACTED]^{(b) (4)}, Document Control No. 930073490) by Wednesday, June 11, 2014, COB. If the report has already been submitted to the NDA, please provide the location within the submission.

PLEASE REPLY BY EMAIL (sammie.beam@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0080). We are providing the above information via electronic mail for your convenience.

Sammie Beam, RPh.
CAPT, U.S. Public Health Service
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SAMMIE G BEAM
06/06/2014



NDA 206353

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Lisa Percival
Director, Global Regulatory Strategy
5 Research Parkway, Mailstop 2CW-506
Wallingford, CT 06492

Dear Ms. Percival:

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: EVOTAZ (atazanavir/cobicistat), tablet, 300mg/150mg

Date of Application: April 4, 2014

Date of Receipt: April 4, 2014

Our Reference Number: NDA 206353

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 June 3, 2013, 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-0080 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Sammie Beam, RPh
CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobials
Center for Drug Evaluation and Research

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/s/

SAMMIE G BEAM
04/17/2014



NDA 206353

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

ATTENTION: Lisa Percival
Director, Global Regulatory Strategy

Dear Ms. Percival:

Please refer to your New Drug Application (NDA) dated and received April 4, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atazanavir (b) (4)/Cobicistat, Tablets, Atazanavir (b) (4) 300 mg/Cobicistat 150 mg.

We also refer to your correspondence dated and received April 4, 2014, requesting a review of your proposed proprietary name, Evotaz. 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 July 3, 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 Sammie Beam, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0080.

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
04/10/2014



IND 117131

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Lisa Percival
Director, Global Regulatory Strategy
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Percival:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for atazanavir and cobicistat fixed dose combination.

We also refer to the telecon between representatives of your firm and the FDA on December 9, 2013. The purpose of the meeting was to discuss plans for and reach consensus on the content and format of the New Drug Application for atazanavir and cobicistat fixed dose combination.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sammie Beam, Regulatory Project Manager, at (301) 796-0080.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: PreNDA

Meeting Date and Time: December 9, 2013 3:00pm to 4:00pm (ET)
Meeting Location: Teleconference

Application Number: IND 117131
Product Name: Atazanavir and cobicistat fixed dose combination
Indication: Treatment of human immunodeficiency virus infection
Sponsor/Applicant Name: Bristol-Myers Squibb Company

Meeting Chair: Mary Singer, MD, PhD, Medical Officer Team Leader
Meeting Recorder: Sammie Beam, RPh, Regulatory Project Manager

FDA ATTENDEES

CDER Participants:

OND/OAP

David Roeder, MS, Associate Director of Regulatory Affairs

OND/OAP/DAVP

Debra Birnkrant, MD, Director, Division of Antiviral Products
Jeffrey Murray, MD, MPH Deputy Director
Mary Singer, MD, PhD, Medical Officer Team Leader
Sarita Boyd, MD Medical Officer
Laine Peyton Myers, PhD, Pharmacology/Toxicology Reviewer
Julian O'Rear, PhD Virology Team Lead
Takashi Komatsu, PhD, Virology Reviewer
Elizabeth Thompson, MS, Chief, Project Management Staff
Sammie Beam, RPh, Regulatory Project Manager

OTS/OCP/DCP4

Islam Younis, PhD, Clinical Pharmacology Team Lead
Vikram Arya, PhD, Clinical Pharmacology Reviewer

ONDQA

Stephen Miller, PhD, CMC Team Leader
Sandra Suarez, PhD, Biopharmaceutics Reviewer

OTS/OB/DB4

Yanming Yin, PhD, Statistician

CDER edata submission group

Lisa Lin

SPONSOR ATTENDEES

Richard Bertz, PhD, Executive Director, Discovery Medicine & Clinical Pharmacology (DMCP)

Ih Chang, PhD, Director, Biostatistics

Todd Correll, PharmD, Atazanavir Development Lead

Marc Davies, PhD, Group Director, Drug Safety Evaluation (DSE)

Margo Heath-Chiozzi, MD, Vice President, GRSS, Virology

Stephen Kaplita, MS, Associate Director, GBS

Thomas Kelleher, PhD, Group Director, Global Biometric Sciences (GBS)

Neuroscience/Virology

Robert Lange, Ph.D, DABT, Senior Research Investigator, DSE

Faranak Nikfar, PhD, Senior Principal Scientist, Drug Product Science and Technology (DPST)

Lisa Percival, MS, Director, GRSS, Virology & US

Barry Scheer, PhD, Associate Director, GRSS CMC

Heather Sevinsky, MS, Senior Research Investigator, DMCP

Chuck Wolleban, US Regulatory

Denise Perniciaro, CMC Regulatory

1.0 BACKGROUND

The purpose of the meeting is to discuss plans for and reach consensus on the content and format of the New Drug Application for an immediate release fixed dose combination of atazanavir and cobicistat for the treatment of human immunodeficiency virus-1 (HIV-1) infection. The current adult dosage form under development for commercialization is an oval (b) (4) film-coated tablet containing 300 mg atazanavir and 150 mg cobicistat for oral administration.

Atazanavir, a protease inhibitor, is currently approved in combination with other antiretroviral agents in HIV-1 infected adults and pediatric patients 6 to <18 years of age in the United States.

Cobicistat is a pharmacokinetic enhancer of antiretroviral agents, including atazanavir. Cobicistat is not currently approved in the United States as an individual drug.

The Division granted this meeting on October 10, 2013. BMS submitted their briefing document on November 1, 2013. Preliminary written responses were sent to BMS on December 5, 2013. On December 6, 2013, BMS responded that they wanted to focus the meeting discussion on the amount of CMC long term stability data in the NDA and to clarify the FDA request for safety datasets and format of the datasets. BMS was informed prior to the meeting that the summary of the high fat BA study and the design of the trial in Question 4 was acceptable and whether the data supports the proposed labeling recommendation regarding BA and food effect will be a review issue.

2.0 DISCUSSION

Question 1: As per the October 2006 FDA Guidance for Industry, entitled “Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV,” plans for submission of an application for a combination product not listed in Attachment B of the Guidance should be discussed with the Division of Antiviral Drug Products prior to submission. Based on the available clinical data to support the co-administration of ATV and COBI and the future NDA resubmission for COBI (Gilead Sciences studies GS-US-216-0105 GS-US-216-0114), a fixed-dose combination (FDC) of ATV and COBI meets the criteria set forth in the referenced Guidance for Industry as follows:

- It will contain two components of an established fully suppressive regimen,
- It will be administered QD,
- It can be recommended as a preferred or alternative regimen component in DHHS treatment guidelines (if COBI is approved as a pharmacoenhancer for use with ATV),
- Clinical efficacy and safety data that support the use of the FDC are available,
- It will be able to be commonly used in treatment-naive patients,

- Individual drug interaction and toxicity profiles have been characterized and allow for concomitant dosing,
- The components of the FDC have compatible food and fluid requirements.

BMS plans to make the ATV/COBI FDC available to [REDACTED] (b) (4), in addition to US marketing, and at the time of the NDA submission, a minimum of 6 months of stability data from registrational long-term term and accelerated studies (LTSS) on three batches of atazanavir sulfate/cobicistat film-coated tablets, 300 mg as free base/150 mg (ATV/COBI) will be provided.

Does the FDA agree that the provisions set forth in the referenced Guidance for Industry, including a priority review designation and submission of an application with a minimum of 6 months of long-term stability data, apply to the proposed FDC?

FDA Response to Q1:

The guidance cited in the background package, “Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV” was issued in 2006 when there was very limited availability of anti-HIV drugs, [REDACTED] (b) (4). This guidance is currently being revised and its scope is under reconsideration. Additionally, we note that this FDC will reduce pill burden for the boosted PI component of an antiretroviral regimen, but it does not contain two or more antiretroviral drugs, and is not considered a complete antiretroviral regimen. Finally, the Cobi component relies upon information from a different pharmaceutical manufacturer, whereas the scope of the ICH guidance on “Stability Testing for New Dosage Forms” (Q1C) is “stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products.”

For these reasons, we recommend that the NDA for atazanavir and cobicistat tablets be supported by 12 months of stability data on 3 batches at submission. We concur with the plans to identify and qualify degradation products in the atazanavir and cobicistat tablet based on the ICH Q3B recommendations.

We will determine standard or priority review designation during the filing review of the submitted application.

Meeting Discussion: BMS inquired whether the FDA would reconsider the need for 12 months of stability data at the time of NDA filing. As an update on stability, BMS has 9 months of stability data on three primary batches and 12 months of data for three supportive batches. They feel the data from the supportive batches will also support the stability. BMS requested the FDA consider 9 months of stability data instead of 12 months of stability data.

With the information currently available, the FDA still recommends 12 months of stability data. However, the FDA advised BMS to submit a short summary of their updated stability data indicating the similarities and differences between the primary and supportive batches. BMS should also include the timelines when the full report of the data will be available. BMS stated they would send it earlier by e-mail and follow up with a submission to the application. FDA noted it would be reviewed in a timely manner.

BMS indicated that all of the elements, except the stability data, are in place for the submission of the NDA at the end of March 2014. At that time they will have only 9 months of stability data. They will have the 12 month stability day in mid-February and will need an additional 1½ to 2 months to complete a full report.

The FDA also indicated that the above referenced Guidance is currently under revision and, with the tentative approval of more than 160 PEPFAR drugs, changes are being discussed internally.

Post Meeting Comments: BMS submitted the summary of the updated stability data and timelines for the full report data by electronic mail on December 11, 2013 and to the application on December 13, 2013. After review by the FDA, we have the following response:

We have evaluated from a risk-benefit perspective the information on the stability batches of the atazanavir and cobicistat (b)(4) tablets. This includes information about the 3 supportive lots (b)(4). Considering the indication, and given the strong similarity of the supportive batches to the primary batches (same formulation, same packaging and comparable manufacturing equipment), we recommend the following approach:

- Submit the NDA with 9 months of primary stability data and 12 months of data on the supportive batches;**
- Update the NDA within 30 days of submission with the 12 month data on the primary batches.**

Question 2: Content of the NDA

At the time of the NDA filing, BMS is planning to provide a minimum of 6 months of stability data from registrational long-term and accelerated studies (LTSS) on three batches of ATV/COBI film-coated tablets, 300 mg as free base/150 mg, as recommended in the October 2006 FDA Guidance for Industry, entitled “Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV”. The ongoing study is based on the ICH guidelines Q1A (R2), Stability Testing of Drug Substance and Products; and Q1B, Photostability testing of New Drug Substance and Products.

Information related to degradation products observed in the ATV/COBI drug product will be included in the NDA, and any degradation product observed during our stability studies conducted at the recommended storage conditions will be identified and qualified when present at levels greater than the reporting threshold as per ICH Q3B(R), Impurities in New Drug Products.

Does the agency concur with this proposal?

FDA response to Q2:

See our response to Question 1 regarding the amount of data at NDA submission. We recommend that the stability studies include 30degC/75%RH as a long-term condition, given the possible use of this product in any climatic zone.

Meeting Discussion: No discussion occurred.

Question 3: In Oct-2011, Bristol-Myers Squibb (BMS) and Gilead Sciences, Inc. (Gilead) entered into a licensing agreement for BMS to develop and commercialize a FDC containing BMS's atazanavir sulfate and Gilead's cobicistat. Under this agreement, Gilead is collaborating with BMS to provide assistance and any required information/data to secure and maintain the registration of the FDC and will be the supplier of the COBI active pharmaceutical ingredient (API) for the manufacture of the FDC. However, BMS is solely responsible for all of the FDC development work, regulatory responsibilities, manufacturing, distribution, and commercialization worldwide. Gilead remains solely responsible for COBI as a stand-alone product and for use in combination with other agents. According to the above-referenced Guidance for Industry, applicants for FDC products may provide clinical efficacy and safety information by referencing their own relevant NDA or IND submission and/or cross-referencing another applicant's submission for which they have been given right of reference. The proposed ATV/COBI FDC NDA submission will include letters of cross reference to the respective Reyataz[®] Capsules and cobicistat Tablets NDAs and cobicistat Drug Master File (if applicable) for support of drug-substance related CMC, nonclinical, and clinical information related to the individual components. In addition, the proposed NDA submission will include:

- Pharmacokinetic (PK) data/results from a bioequivalence study AI424511
- CMC information related specifically to the development and manufacture of the FDC tablet
- Nonclinical information to support qualification of impurities identified with the FDC that were not previously qualified for either of the individual components.

Does FDA agree with the proposed content to support the ATV/COBI NDA submission?

FDA Response to Q3:

CMC:

We acknowledge that information about the atazanavir and cobicistat drug substances will be cross-referenced to other NDAs or DMFs. Letters of Authorization should be provided for all cross-references to other NDAs or DMFs.

If information about the manufacture of the cobicistat (b) (4) is being referenced to a Gilead submission, it is important that you identify the date of that submission, and the specific processes that are being cross-referenced. This would also apply if information about the manufacture of the atazanavir (b) (4) is being referenced to the Reyataz Capsule NDA.

Clinical:

Please include safety results from the bioequivalence study AI424511.

Clinical Pharmacology:

The Sponsor's proposal for including results from BE trial AI424511 is acceptable.

Biopharmaceutics:

Refer to our responses to Q4 in terms of the acceptability of bioequivalence study AI424511.

Meeting Discussion: No discussion occurred.

Question 4: Study AI424511 was designed to evaluate the bioequivalence of ATV 300 mg in a FDC tablet of ATV/COBI 300/150 mg and the relative bioavailability of COBI as compared to a 300 mg ATV capsule co-administered and a 150 mg COBI tablet, respectively, when administered with a light meal. This assessment was conducted under fed conditions as it is recommended that ATV be taken with food. In addition, this study also assessed the relative bioavailability of ATV and COBI in the FDC as compared to co-administration of the individual components under fasted conditions. Finally, the effects of a high fat meal on the PK of ATV and COBI in the FDC relative to fasting were assessed. This study was a 5-period, randomized study in healthy volunteers, depicted in Table 3.2-1. First patient first visit occurred 29-Apr-2013. Sixty-four subjects were randomized, and 62 subjects completed the study.

Table 3.2-1: Study Design for AI424511

Days	Periods 1 and 2			Was h-out up to Day 14	Periods 3 and 4			Wash-out up to Day 28	Period 5	
	Day 1	Was h-out up to Day 8	Day 8		Day 15	Was h-out up to Day 22	Day 22		Day 29	Day 31
-21 to -1										

S & E	Treatment A or B		Treatment B or A		Treatment C or D		Treatment D or C		Treatment E	Discharge
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S&E = screening and enrollment

Treatment A: ATV 300 mg capsule + COBI 150 mg tablet co-administered following a light meal
 Treatment B: ATV/COBI 300/150 mg FDC tablet administered following a light meal
 Treatment C: ATV 300 mg capsule + COBI 150 mg tablet co-administered under fasted conditions
 Treatment D: ATV/COBI 300/150 mg FDC tablet administered under fasted conditions
 Treatment E: ATV/COBI 300/150 mg FDC tablet administered following a high fat meal

Results of the comparison of PK parameters of ATV and COBI in the FDC to those when the individual components are co-administered when given with a light meal are provided in Table 3.2-2.

Table 3.2-2: Statistical Analyses of ATV and Cobicistat PK Parameters in the FDC Tablet Compared to Co-administration of the Individual Components When Given with a Light Meal

Pharmacokinetic Parameter	Adjusted Geometric Means		GMR (90% CI)
	Treatment A: ATV + cobicistat (Reference) [N = 63]	Treatment B: ATV/cobicistat FDC (Test) [N = 62]	
Atazanavir (with a light meal)			
C _{max} (ng/mL)	3822	4101	1.073 (1.012, 1.137)
AUC _(INF) (ng.h/mL)	33475	35623	1.064 (1.011, 1.120)
AUC _(0-T) (ng.h/mL)	32723	34848	1.065 (1.012, 1.120)
Cobicistat (with a light meal)			
C _{max} (ng/mL)	1320	1351	1.023 (0.991, 1.057)
AUC _(INF) (ng.h/mL)	9053	9225	1.019 (0.982, 1.058)
AUC _(0-T) (ng.h/mL)	8745	8912	1.019 (0.983, 1.057)

GMR = geometric mean ratio
 CI = confidence interval

Preliminary data demonstrate that ATV exposures are bioequivalent between the ATV/COBI FDC tablet and co-administration of the individual components when given with a light meal. Although not a primary endpoint for determination of bioequivalence, ATV C₂₄ (plasma concentration 24 hours post-dose) in the FDC also met bioequivalence criteria to ATV C₂₄ when the individual components were co-administered following a light meal. The GMR (90% CI) for ATV C₂₄ was 1.084 (1.014, 1.158).

Finally, though an objective of study AI424511 was to assess the bioavailability of COBI in the FDC relative to co-administration of the individual components when given with a light meal, data demonstrate that COBI exposures from the FDC are bioequivalent to those from the COBI tablet when co-administered with the ATV capsule given with a light meal.

Secondary objectives of study AI424511 also included assessment of the bioavailability of ATV and COBI in the FDC compared to co-administration of the individual components under fasted conditions. Results for this analysis are provided in Table 3.2-3.

Table 3.2-3: Statistical Analyses of ATV and Cobicistat PK Parameters in the FDC Tablet Compared to Co-administration of the Individual Components Under Fasted Conditions

Pharmacokinetic Parameter	Adjusted Geometric Means		GMR (90% CI)
	Treatment C: ATV + cobicistat [N = 63]	Treatment D: ATV/cobicistat FDC [N = 63]	
Atazanavir			
C _{max} (ng/mL)	2588	2942	1.137 (1.000, 1.292)
AUC _(INF) (ng.h/mL)	25532	28341	1.110 (0.991, 1.244)
AUC _(0-T) (ng h/mL)	25004	27841	1.113 (0.993, 1.248)
Cobicistat			
C _{max} (ng/mL)	952	1033	1.085 (0.925, 1.273)
AUC _(INF) (ng.h/mL)	7582	7398	0.976 (0.886, 1.075)
AUC _(0-T) (ng.h/mL)	6534	7199	1.102 (0.929, 1.307)

Preliminary data indicate that ATV AUC_(INF) and AUC_(0-T) from the FDC meet *bioequivalence criteria (90% CI between 0.80 and 1.25) when compared to co-administration of the individual components under fasted conditions*; however the upper bound for ATV C_{max} are just slightly above 1.25. Similarly, COBI AUC_(INF) from the FDC meets bioequivalence criteria when compared to co-administration of the individual components under fasted conditions;

however the upper bounds for COBI Cmax and AUC(0-T) are also just slightly above 1.25. Study AI424-511 was not powered to assess bioequivalence under fasted conditions. It will be recommended that the ATV/COBI FDC be taken with food. The variability of both ATV and COBI are higher under fasted conditions relative to administration with a light meal, and this increased variability was the likely reason for the wider confidence intervals around the geometric mean. Nevertheless, these data demonstrate that with respect to exposures to ATV and COBI, the FDC also performs similarly to co-administration of the individual components under fasted conditions.

Additional details will be provided in the background information to be submitted within 30 days of the assigned pre-NDA meeting date. Study AI424511 also assessed the effect of food (a high fat meal) on the exposures to ATV and COBI in the FDC relative to fasted conditions. These data are not yet available; however will be provided in the NDA.

Does FDA consider the BE study data acceptable to support the proposed indication for the upcoming ATV/COBI fixed dose combination tablet submission?

FDA response to Q4:

Biopharmaceutics Response:

In general, a BE study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. However, since the proposed product is intended to be administered under fed conditions only, the Agency may consider the BE results under fed conditions. This requires information on the effect of high fat meal on the BA of your proposed product. Therefore, the acceptability of the study design (e.g. under light fat meal) as the basis for approval of your proposed product will be determined once the results of the effect of high fat content on the BA of your proposed product are submitted and reviewed. In addition, the results of the fasted BE study and its relevance on regulatory decision making will be a review issue.

Meeting Discussion: No discussion occurred.

Question 5: For submission of data sets that support the assessments of bioequivalence and food effect of the fixed dose combination of ATV and COBI, BMS proposes to submit SAS datasets for demographics, exposure, disposition, plasma concentrations of both ATV and COBI, and PK derived parameters based on BMS proprietary structure and formats in order to be consistent with previous submissions for ATV.

Does FDA concur?

FDA response to Q5:

Clinical:

Please submit safety data sets for the fixed dose combination of ATV and COBI.

Meeting discussion: The FDA clarified that the standard safety sets from the BE study are being requested.

eData:

The Agency prefers sponsors to submit datasets based on the [Study Data Specifications](#) (currently 2.0). However, in general, the Agency accepts datasets, which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance; based on the timing of protocol design, protocol initiation, and data collection.

The Agency expects sponsors to evaluate the risk involved converting study data collected to standardized data, if applicable. The Agency prefers sponsors to submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario; decision rationale for not converting or decision rationale for converting. The Agency expects sponsor's evaluation and rationale to include study data scientifically relevant to the application's safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The [PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017](#) guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsors should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. Sponsors should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (CDASH) standard for design and implementation of data collection instruments.

The Agency's methodology and submission structure supports research study design, as indicated in the [Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications](#) and the [Study Data Specifications](#). The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. Sponsors should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See [SEND](#), [SDTM](#) and [ADaM](#) as referenced in [Study Data Specifications](#)). Study analyses datasets should be traceable to the tabulations datasets. In addition, please reference the [CDER Common Data Standards Issues Document](#) for further information on data standardization in submissions.

Additional Links:

[Electronic Regulatory Submissions and Review Helpful Links](#)

[Electronic Common Technical Document \(eCTD\)](#)

[Study Data Standards Resources](#)

Meeting Discussion: At this time, the FDA will accept the proprietary BMS format for submitting datasets to the new NDA as long as it is consistent with previous BMS submissions.

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

We acknowledge your initial Pediatric Study Plan submitted on September 27, 2013.

4.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements of Prescribing Information](#) website including the Final Rule (Physician Labeling

Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

5.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

6.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

7.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
BMS will submit a summary of the stability data including scale and timelines for the 12 month data. The FDA will review this updated information in a timely manner.	BMS	FDA received via e-mail on December 11, 2013 and by submission to the application on December 13, 2013.

8.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting.

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

/s/

DEBRA B BIRNKRANT
12/20/2013