

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206353Orig1s000

MEDICAL REVIEW(S)

Clinical Review

Date	December 19, 2014
From	Sarita Boyd, Pharm.D.
Subject	Clinical Review
NDA/BLA #	NDA 206353
Supplement#	
Applicant	Bristol Myers Squibb
Date of Submission	April 4, 2014
PDUFA Goal Date	February 4, 2015
Proprietary Name / Established (USAN) names	Evotaz (atazanavir/cobicistat)
Dosage forms / Strength	Tablet / 300 mg of atazanavir and 150 mg of cobicistat
Proposed Indication(s)	Fixed dose combination indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults
Recommended:	Approval

1. Background

The Applicant is proposing approval of a FDC product containing atazanavir (ATV) and cobicistat (COBI), two approved drugs. Atazanavir (ATV) is an HIV protease inhibitor (PI) approved alone and in combination with low-dose ritonavir (RTV), a cytochrome P450 3A (CYP3A) inhibitor that increases ATV exposure. Cobicistat (COBI) received approval on September 24, 2014 as a CYP3A inhibitor indicated to increase systemic exposure of ATV or darunavir (DRV) in combination with other antiretroviral agents for treatment of HIV-1 infection.

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. Safety and efficacy data from clinical trials conducted with ATV/co as single agents were reviewed as part of the COBI NDA and were not required for this NDA.

2. Clinical Pharmacology/Biopharmaceutics

The development program for ATV/co FDC is based on comprehensive development and approval of ATV and COBI as single agents and pharmacokinetic (PK) bridging of ATV/co FDC to the single agents. Trial AI424511 evaluated BE/BA of ATV and of COBI in a FDC of ATV/co compared to ATV and COBI as single agents in 64 healthy subjects following a light meal and under fasted conditions. Additionally, Trial AI424511 assessed the effect of a high-fat meal on the PK of ATV and COBI when administered as a FDC. Overall, Trial AI424511 showed acceptable exposures of ATV and COBI when administered as a FDC compared to

single agents. Please refer to the Clinical Pharmacology Review by Dr. Leslie Chinn for complete details.

3. CMC

Bristol-Myers Squibb (BMS) co-formulated ATV ((b) (4)) 300 mg and COBI 150 mg using the COBI formulation (b) (4) developed by Gilead and using (b) (4) . ATV/co FDC tablet contains the following inactive ingredients: stearic acid, microcrystalline cellulose, sodium starch glycolate, crospovidone, hydroxypropyl cellulose, magnesium stearate, and croscarmellose. The coating agent (b) (4) Pink is composed of hypromellose, titanium dioxide, triacetin, talc, and iron oxide (red). The proposed shelf life is 24 months at room temperature in all climatic zones. Please refer to the CMC Review by Dr. George Lunn for complete details.

4. Clinical Efficacy and Safety

The efficacy of ATV and COBI administered as single agents was evaluated in the pivotal Phase 3 trial GS-US-216-0114, a randomized, double-blind, active-controlled trial in HIV-infected treatment-naïve adults. Safety was evaluated using the pooled results from the pivotal Phase 3 trial and the Phase 2 trial GS-US-216-0105. These trials supported approval of COBI for use in combination with ATV. Please refer to Dr. Peter Miele's clinical review of the cobicistat NDA (203094) for complete details. Efficacy and safety of ATV and COBI as single agents is extrapolated to ATV/co FDC with bridging PK data summarized in Section 2 of this review.

Limited safety data from Trial AI424511, conducted in 64 healthy subjects, did not generate any new safety concerns for atazanavir coadministered with cobicistat. Subjects in this trial received single doses of atazanavir and cobicistat (FDC or individual agents) on Day 1, 8, 15, and 22, and some on Day 29 with 7-day washout periods in between each dose. There were no deaths, serious adverse events, or discontinuations due to adverse events (AE), and all AEs were mild or moderate. The most common AEs were dizziness (6%), abdominal discomfort (5%), musculoskeletal chest pain (5%), and nasopharyngitis (5%). AEs were either consistent with the known safety profile of atazanavir and cobicistat or not drug-related per the investigator.

5. Pediatrics

The NDA does not contain pediatric data. The Applicant submitted the Agreed Initial Pediatric Study Plan for ATV/co FDC; the Agency previously agreed with the Applicant's planned waiver and deferral requests. The Applicant submitted a partial waiver request for children < 3 months of age and a deferral request for children ≥ 3 months to (b) (4) 18 years of age. A partial waiver for children < 3 months of age is necessary because of the risk of kernicterus (b) (4) in this age group. The deferral request is reasonable (b) (4)

(b) (4). The deferral and waiver requests will be reviewed by the Pediatric Review Committee (PeRC) on December 17, 2014.

6. Labeling

Overall, the following edits were made throughout the ATV/co label:

- Updates to maintain consistency with the COBI label as it pertains to ATV/co.
- Removal of (b) (4) clinical trial, postmarketing, and/or drug interaction data from ADVERSE REACTIONS, MICROBIOLOGY, CLINICAL PHARMACOLOGY, and CLINICAL STUDIES sections. Data from Trials GS-US-216-0114 and GS-US-216-0105 were retained because these trials are directly relevant for both components of ATV/co FDC.

Additional major revisions proposed to the Applicant are as follows:

U.S. Package Insert (USPI)

DOSAGE AND ADMINISTRATION

Deletion of the statement, "EVOTAZ (b) (4)

(b) (4)

In the absence of formulation concerns or data, this statement should be deleted from labeling. This approach is consistent with other FDC antiretroviral labels and DAVP's current perspective on this issue.

CONTRAINDICATIONS

- Addition of lurasidone based on recommendations from the Division of Psychiatry Products in response to a consult request.
- Removal of "ritonavir or products containing ritonavir." This recommendation was placed in Section 5.

WARNINGS AND PRECAUTIONS

- Simplification of "Cardiac Conduction Abnormalities" and "Rash," (b) (4)
- Addition of "Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions," similar to the cobicistat label.

- Addition of “Antiretrovirals that are Not Recommended” which include other antiretroviral drugs that require pharmacokinetic boosting (i.e., another PI or elvitegravir) and products containing ATV, COBI, or RTV.
- Removal of [REDACTED] (b) (4)

DRUG INTERACTIONS

- Alignment of recommendations with the COBI label
- Recommendation not to coadminister ATV/co with apixaban. The dosage recommendation for apixaban with strong CYP3A inhibitors (as stated in the apixaban label) may result in underdosing of apixaban with ATV/co.
- Addition of recommendations for coadministration with dabigatran.

U.S. Patient Package Insert (USPPI)

Removal of the [REDACTED] (b) (4)

7. Recommendations/Risk Benefit Assessment

I recommend approval of atazanavir/cobicistat 300/150 mg tablet, a fixed-dose HIV protease inhibitor and CYP3A inhibitor that increases systemic ATV exposures, in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The recommendation is based on the BE of the ATV/co FDC tablet compared to the approved single-agent products ATV and COBI for the same indication. The BE/BA trial results show the risk benefit assessment is favorable and similar to that of the individual, approved components.

A PMR will be issued for pediatric studies under the Pediatric Research Equity Act (PREA) and consistent with the Agreed Initial Pediatric Study Plan. No additional PMRs are recommended. Of note, PMRs are in place for COBI (with ATV) for pediatric studies [REDACTED] (b) (4)

Clinical Review
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 NDA 206353
 Evotaz (atazanavir/cobicistat)

APPENDIX

Clinical Investigator Financial Disclosure

Application Number: 206353
 Submission Date(s): April 4, 2014
 Applicant: Bristol-Myers Squibb
 Product: atazanavir/cobicistat

Reviewer: Sarita Boyd, Pharm.D.
 Date of Review: December 19, 2014
 Covered Clinical Study (Name and/or Number): AI424-511

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>5</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

All investigators reported having no disclosed financial interests/arrangements. Financial disclosure information does not affect approvability of this application.

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

/s/

SARITA D BOYD
12/22/2014

MARY E SINGER
12/22/2014

I concur with Dr. Boyd's review and recommendations.