

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206353Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

NDA	206353
Submission Type	505(b)(2)
Applicant	Bristol-Myers Squibb
Submission Date	April 4 th , 2014
Generic Name	Atazanavir/ Cobicistat
Trade Name	Evotaz TM
Dosage Form (Strength)	FDC Tablet (Atazanavir 300 mg / Cobicistat 150 mg)
Proposed Indication	Treatment of HIV-1 infection in adults in combination with other antiretroviral agents
CDTL	Islam R. Younis, Ph.D.
Recommendation	Approval

1. Introduction

Atazanavir (ATV) is an HIV protease inhibitor, coadministered with or without ritonavir (RTV), that was initially approved for treatment of HIV-1 in combination with other antiretroviral agents in 2003. ATV is currently available as capsules (150, 200, and 300 mg) and as an oral powder for use in pediatric patients 3 months and older weighing at least 10 Kg.

Cobicistat (COBI) was initially approved in 2012 as part of StribildTM, four drugs fixed dose combination (FDC) tablet for the treatment of HIV. It was later approved as a single agent in 2014 for the indication of increasing systemic exposure of ATV or darunavir (once daily dosing regimen) in combination with other antiretroviral agent in treatment of HIV-1 infection. Cobicistat is a strong CYP3A inhibitor and has no antiretroviral activity.

2. Background

The Applicant developed a FDC tablet containing ATV 300 mg and COBI 150 mg. The proposed indication is treatment of HIV-1 infection in combination with other antiretroviral agents.

The efficacy of the ATV/COBI combination was established based on the individual approved products administered as single agents in a randomized, double-blind, active-control phase III trial (Trial GS-US-216-0114) which compared the safety and efficacy ATV/COBI (300 mg/150 mg) to that of ATV/RTV (300 mg/100 mg) in 692 HIV infected treatment-naïve adults. In this study, the difference in the percentage of patients who achieved HIV-1 RNA < 50 copies/mL at Week 48 between the ATV/COBI and ATV/RTV treatment arms was -2.2% [95% CI of -7.4 to 3%]. The Safety of the combination was evaluated using the pooled safety data from the above-

mentioned phase III trial and a phase II trial (Trial GS-US-216-0105), as reviewed in NDA 203094.

The findings of this study was extrapolated to HIV-1 treatment-experienced patients because the approved regimens are the same in both populations (ATV 300 mg plus RTV 100 mg QD) and because ATV exposures following coadministration with RTV 100 mg or COBI 150 mg are expected to be similar (please refer to the Clinical Pharmacology Review of NDA 203094).

Based on the above, a clinical trial to evaluate the efficacy and safety of ATV/COBI FDC was not required. The Applicant is seeking approval of the current application based on the results of a single relative bioavailability and food effect study (Study AI424511) where the pharmacokinetics of ATV and COBI were compared following the administration of ATV and COBI as single agents vs. the administration of ATV/COBI FDC.

3. Chemistry, Manufacturing, and Control

The NDA is recommended for approval from CMC perspective. All CMC, Biopharmaceutics, and Quality Microbiology issues concerning the drug product have been satisfactorily resolved. An overall recommendation of Acceptable has been made by the Office of Compliance. Please refer to the CMC review by Drs. Lunn, Miller, and Madurawe and biopharmaceutics review by Drs. Hughes and Dorantes for full details.

Drug Substance: The ATV drug substance used to manufacture the FDC tablets is the same as that used for the approved Reyataz[®] capsules, and reference is made to NDA 21567 for drug substance CMC. There are no atazanavir-derived degradants. Reference is also made to Gilead Sciences' DMF #25188 for CMC information regarding the COBI on silicon dioxide drug substance. The cobicistat impurities are mostly the same as those found in previous approved products although in some cases the limits are higher. Additionally 4 new cobicistat-related impurities are found. The applicant has conducted a 3 month oral rat study to qualify these impurities. The impurity acceptance criteria were tightened during the review process.

Drug Product: The drug product is an immediate release tablet. It consists of an oval pink biconvex film-coated (b) (4) tablets debossed with 3641 on one side and plain on the other. Each (b) (4) tablet contains 300 mg ATV as the free base and 150 mg COBI. (b) (4)

A shelf life of 24 month is granted under storage conditions of at 20° to 25°C (68° to 77°F) with excursions permitted between 15° to 30°C (59° to 86°F). The drug product specification contains

tests for appearance, identity, content uniformity, assay, impurities, dissolution, and microbial limits are acceptable as amended. The analytical methods are described in reasonable detail and have been validated.

Packaging: The tablets are packaged 30 count in (b) (4) HDPE bottles containing (b) (4) silica gel desiccant. The bottles are (b) (4) and child-resistant closures. Each component of the container-closure system complies with the appropriate 21 CFR food additive regulations.

4. Nonclinical Pharmacology/Toxicology

The NDA is recommended for approval from pharmacology and toxicology perspective. Please refer to the pharmacology and toxicology review by Drs. Myers, Powley and Ghantous for full details.

The applicant submitted a 3-months toxicity study in Sprague-Dawley rats to qualify (b) (4) impurities (b) (4). The study results and quantitative structure-activity relationship predictions of mutagenicity indicate that the COBI drug substance is within specifications accepted under NDA 203-100.

No other new pharmacology/toxicology studies were submitted to the NDA and there have been no new safety concerns based on non-clinical studies identified with ATV or COBI.

5. Clinical Pharmacology

The NDA is recommended for approval from clinical pharmacology perspective. Please refer to the clinical pharmacology review by Drs. Chinn and Younis for full details.

The pivotal trial for this NDA was a randomized, single-dose, 5-period, crossover relative bioavailability study which compared the pharmacokinetics of ATV and COBI following the administration of ATV 300 mg and COBI 150 mg together as single agents and the administration of ATV/COBI 300/150 mg FDC under fasted or fed (light meal) conditions in 64 healthy volunteers (Study AI424511). The study also evaluated the effect of light meal and high-fat meal on the pharmacokinetics of ATV/COBI following the administration of the FDC.

Administration of the FDC with a light meal resulted in similar exposures of both ATV and COBI compared to administration of the single agents (90% CI for ATV C_{max}, AUC_t, and C₂₄ and for COBI C_{max} and AUC_t within the BE limits of 80-125%). Under fasted conditions, the FDC provided slightly higher exposures of both ATV and COBI compared to the single agents

(90% CI for ATV C_{max}, AUC_t, and C₂₄ and for COBI C_{max} and AUC_t ranging from 93-131%). This slight increase in ATV exposure under fasted conditions is not considered clinically significant and does not pose safety concerns to the patients if the FDC was accidentally administered under fasted conditions.

Administration of the ATV/COBI FDC with a light meal significantly increased ATV AUC by 28%, while administration of the FDC with a high-fat meal numerically reduced ATV AUC by ~4%. The clinical pharmacology review team concurs with the Applicant's proposal to administer the FDC with food, consistent with the current prescribing information of ATV, based on the following:

1. Higher ATV trough concentrations (the clinically relevant parameter for efficacy) observed following the FDC administration under fed conditions relative to fasted conditions.
2. Bioequivalence was established between the FDC and ATV/RTV singles agents under light meal conditions.

Inspections of the clinical and bioanalytical sites for Study AI424511 were requested and were not conducted. The Office of Scientific Investigations determined that inspections were not necessary because both the clinical and bioanalytical sites had been inspected recently and no issues were noted. Please refer to Drs. Mada, Choi, Haider, and Tayler memorandum dated 07/14/2014.

6. Clinical Microbiology

The NDA is recommended for approval from clinical virology perspective. Please refer to the clinical virology review by Drs. Komatsu and O'Rear for full details.

The Applicant did not conduct any new nonclinical virology studies for this submission. All of the nonclinical virology data have been submitted with the Reyataz[®] submission (NDA 21567) and the Stribild[™] submission (NDA 203100).

7. Clinical Efficacy and Safety

The NDA is recommended for approval from clinical perspective. Please refer to the clinical review by Drs. Boyd and Singer for full details.

The applicant did not conduct any new clinical efficacy trials to support this application. The approval of this application is based on the pivotal BE study (see clinical pharmacology). There were no new safety concerns observed for the ATV/COBI combination in the pivotal BE study.

There were no deaths, serious adverse events, or discontinuations due to adverse events (AE), and all AEs were mild or moderate.

8. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

9. Pediatrics

There are no pediatric data in the application. In the Agreed Initial Pediatric Study Plan dated 02/07/2014 for ATV/COBI FDC the Agency agreed with the Applicant on the following:

1. Waive the requirements to evaluate ATV/COBI FDC in pediatrics < 3 months of age because of the risk of ATV related kernicterus in this age group.

(b) (4)

10. Other Relevant Regulatory Issues

Financial disclosures were obtained for the pivotal bioequivalence trial for all of the clinical investigators (n=5) and were reviewed by Dr. Boyd. All investigators reported having no disclosed financial interests/arrangements and therefore, financial disclosure information does not affect approvability of this application.

11. Labeling

The proposed proprietary name EVOTAZ for ATV/COBI FDC was considered acceptable by DMEPA and DAVP. One issue raised by DMEPA was the inconsistency in communicating (b) (4). DMEPA noted that this information appears in the Recommended Dosage (Section 2.1) and in the Patient Counseling Information (Section 17) (How should I take Evotaz) and is missing from the Highlights of Prescribing Information section of the labeling and the container label. DMEPA recommended adding these instructions to the Highlights of Prescribing Information and to the container label. However, DAVP recommended that the statement be removed from the FPI because the Applicant had no specific data to support the statement. Such statement should be reserved for cases where there is an identified or predicted concern, (b) (4) products. The Applicant agreed to remove this information from labeling

Other revisions to the label included:

1. Adding information to the label regarding baseline resistance in treatment-experienced subjects similar to the language in section 1 of the currently approved label for ATV.
2. Updating the label to maintain consistency with the COBI label.
3. Removal of [REDACTED] (b) (4) from various sections throughout the label because it is not relevant to this combination. Only information relevant to ATV/COBI combination was retained throughout the label.
4. Updating the list of contraindicated drugs:
 - a. Lurasidone was contraindicated for all patients following a consult with the Division of Psychiatry Products.
 - b. Colchicine was contraindicated for patients with renal or hepatic impairment.
5. Drug Interaction:
 - a. Recommendation not to co-administer ATV/COBI with apixaban because of potential under dosing of apixaban when administered with ATV/COBI.
 - b. Addition of recommendations for coadministration with dabigatran.
6. Updating the Warnings and Precautions section as follows:
 - a. Simplification of “Cardiac Conduction Abnormalities” and “Rash,” including [REDACTED] (b) (4).
 - b. Addition of “Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions,” similar to the cobicistat label.
 - c. 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.
 - d. Removal of [REDACTED] (b) (4).
7. Removal of the [REDACTED] (b) (4). The patient labeling review team concurs with this recommendation.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action: Approval

12.2 Risk Benefit Assessment: The risk-benefit profile of ATV/COBI FDC is acceptable based on the assessment of the review team. Because ATV/COBI FDC combination produced similar exposure to the ATV/COBI single agents when given together, the risks and benefits of the ATV/COBI FDC is considered similar to those of the ATV/COBI single agents administered together. Efficacy and safety of ATV/COBI combination as single agents was established previously in clinical trial in HIV-1 treatment naïve patients.

12.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies:
None

12.4 Recommendation for other Postmarketing Requirements and Commitments: A PMR will be issued for pediatric studies under the Pediatric Research Equity Act (PREA) and consistent with the Agreed Initial Pediatric Study Plan.

12.5 Recommended Comments to Applicant: None

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/s/

ISLAM R YOUNIS
01/14/2015