

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203094Orig1s000

203094Orig2s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 11, 2014

Reviewer(s): Felicia Duffy, RN, BSN, MEd
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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Tybost (cobicistat), 150 mg

Therapeutic Class: CYP3A Inhibitor

Dosage and Route: One tablet by mouth once daily

Indication: To increase systemic exposure of atazanavir and darunavir in
the treatment of HIV-1 infection in adults

Application Type/Number: NDA 203094

Applicant/sponsor: Gilead Sciences, Inc.

OSE RCM #: 2014-791

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for cobicistat (COBI), a structural analogue of ritonavir (RTV) and does not exhibit antiretroviral activity. On June 27, 2012, the Agency received an original NDA from Gilead Sciences for COBI, as an individual drug product indicated as a pharmacokinetic enhancer of the HIV-1 protease inhibitors atazanavir (ATV) or darunavir (DRV). This is a review of a resubmission of the application after it initially received a Complete Response (CR) in April 2013. The Applicant did not submit a proposed REMS or risk management plan for COBI.

1.1 DISEASE BACKGROUND¹⁻³

Human Immunodeficiency Virus (HIV) is a ribonucleic acid (RNA)-containing virus that uses the enzyme reverse transcriptase to copy its RNA into the host cell DNA. It attacks the immune system by destroying the body's immune system (CD4 cells). HIV progressively destroys the body's ability to fight infections and certain cancers. An estimated 1.1 million people in the United States are living with HIV. Worldwide, an estimated 35.5 million people are living with HIV. Early diagnosis of HIV infection and antiretroviral therapy are associated with reduced morbidity and mortality as well as reduced transmission.

Reducing the level of HIV in a person's body to a very low or undetectable viral load (<200 copies/mL) is a primary goal of HIV treatment. The goal is best accomplished by using effective antiretroviral replacement therapy (ART) to maximally inhibit HIV replication. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life. Additionally, effective ART can reduce viremia and transmission of HIV by more than 96%.

The recommendation for the optimal initial ART regimen for a treatment-naïve patients consists of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a drug from one of the three drug classes: a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI) boosted with RTV, or an integrase strand transfer inhibitor (INSTI).

1.2 PRODUCT BACKGROUND

COBI is a structural analogue of the HIV-1 protease inhibitor ritonavir (RTV) but does not exhibit antiretroviral activity. It is a CYP3A inhibitor that enhances or "boosts" the exposure of the HIV-1 protease inhibitors ATV and DRV. The recommended dose is one tablet once daily, which must be co-administered with ATV or DRV (at the same time), and in combination with other HIV-1 antiretroviral agents. Similarly, ATV and DRV must also be co-administered with

¹ Turning the Tide on HIV, Division of HIV/AIDS Prevention, Annual Report 2013. CDC, National Center for HIV/AIDS, Viral Hepatitis STD and TB Prevention, July 2014.

² Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Section accessed August 18, 2014.

³ Maartens, G., Celum, C., and Lewin, S. HIV infection: Epidemiology, Pathogenesis, Treatment and Prevention. *The Lancet*, 2014; vol 384, Issue 9939 (July 19-25): 258-271.

RTV. COBI is currently approved for use as a component of a 4-drug fixed-dose combination product, Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate), indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment naïve (NDA 203100 – approved August 27, 2012). Stribild is not approved with a REMS.

1.3 REGULATORY HISTORY

On June 27, 2012, the Agency received an original NDA from Gilead Sciences for COBI indicated to increase systemic exposures of ATV and DRV in the treatment of HIV-1 infection adults. The original NDA submission for COBI received a Complete Response on April 26, 2013, due to the results from facility inspection findings. The Applicant resubmitted their NDA application on March 28, 2014.

The Applicant did not submit a proposed REMS with this application. However, the Applicant has voluntarily committed to a multi-tiered, broad education plan (targeting pharmacists and HIV health care providers) outside of a REMS, to coincide with the anticipated approval to help reduce the risk of inappropriate use of COBI tablets. The Applicant will provide proactive communications to help educate providers on the correct use of COBI tablets. (b) (4)

2 MATERIALS REVIEWED

- FDA Meeting Preliminary Comments for Cobicistat (IND 101283). March 27, 2012,
- Gilead Sciences Original NDA 203094 submission for Cobicistat. June 28, 2012
 - Section 2.5: Clinical Overview
 - Section 2.7: Clinical Summary
- Peter Miele, MD. DAVP Clinical Review for NDA 203094. March 22, 2013,
- Peter Miele, MD. DAVP Medical Officer’s Review of Proposed Safety Update for NDA 203094. September 10, 2013
- FDA Mid-Cycle Communication Meeting Minutes; no REMS recommended. February 11, 2014
- Sarita Boyd, Pharm.D. DAVP Clinical Review for NDA 203094. August 1, 2014
- Gilead Sciences Draft Prescribing Information for Cobicistat. August 12, 2014

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The Applicant conducted 12 trials involving COBI. However, clinical data from the pivotal Phase 3 Study (GS-US-216-0114) and the supportive Phase 2 Study (GS-US-216-0105) provided the primary data for the characterization of the tolerability, safety, and effectiveness of a COBI-boosted regimen (ATV/COBI) in HIV-infected, antiretroviral treatment naïve subjects. Both studies are randomized, double blind, non-inferiority multicenter safety and efficacy trials. Study GS-US-216-0105 also contains an open-label extension phase after Week 60 [ATV/COBI + Truvada (TVD)] which is ongoing.

The primary efficacy endpoint for Study GS-US-216-0114 was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 supported by the Week 48 data from Phase 2 Study GS-US-216-0105. Only data from Study GS-US-216-0114 is used and reported in the labeling.

- The GS-US-216-0105 (Phase 2), compared a regimen containing ATV/COBI vs. ATV/RTV, each administered with TVD in 79 HIV-1 infected, antiretroviral treatment-naïve adults. Eighty-two percent of subjects in the ATV/COBI group and 86.2% of subjects in the ATV/RTV group had HIV-1 RNA < 50 copies/mL at Week 48 (p-value=0.55).
- In GS-US-216-0114 (Phase 3), the efficacy and safety of ATV/COBI vs. ATV/RTV, each administered with TVD was evaluated for 48 weeks in 692 infected, treatment-naïve adults. 85.2% of subjects in the ATV/COBI group achieved the primary endpoint of HIV RNA < 50 copies/mL at Week 48 compared with 87.4% of subjects in the ATV/RTV group (p-value=0.40).

In summary, Study GS-US-216-0114 demonstrated the efficacy of ATV/COBI administered with TVD for 48 weeks in treatment naïve patients and Study GS-US-216-0105 supported the efficacy the ATV/COBI regimen in HIV-1 infected, antiretroviral treatment naïve adults.

3.2 SAFETY CONCERNS

The most frequently reported adverse events (AEs) in the ATV/COBI treatment group (with comparable rates of each AE in the ATV/RTV group) were jaundice (5% vs. 3%), ocular icterus (3% vs. 1%), nausea (2% vs. 2%) and diarrhea (2% vs 1%).

3.2.1 Serious Adverse Events

In the original NDA submission, nonfatal serious adverse events (SAEs) of any nature were reported in the pooled Phase 2 and Phase 3 trials [38/394 patients (10%) in the ATV/COBI group and 25/377 (7%) in the ATV/RTV group]. Since the original NDA, as provided in the safety update, 25 (6.3%) additional subjects in the ATV/COBI group experienced any treatment-emergent SAE compared to 22 (5.8%) in the ATV/RTV group during the double-blind phase. The clinical reviewer indicated that the events revealed no new safety concerns, and were either unlikely related to ATV/COBI, consistent with AEs occurring with ATV/RTV, or consistent with the proposed labeling as it pertains to AEs associated with protease inhibitors. The incidence of SAEs was slightly higher in the ATV/COBI group compared with the ATV/RTV group, but no distinctive pattern was noted between the two groups with respect to SAEs. SAEs considered related to treatment were infrequent and comparable between the treatment groups.

No deaths were reported in either treatment group during the double-blind randomized period. One death was reported in the ATV/COBI group early in the open-label phase of Study GS-US-216-0105; however, based on limited secondary sources, this death was not likely related to study drug.

3.2.2 Severe adverse events

In the original submission, a total of 56 drug-related adverse events (AEs) of Grade 3-4 severity were reported among 44 (6%) subjects. A relatively low percentage of subjects in either treatment group discontinued study drug to due to a treatment-emergent AE (7%); the most common AEs leading to study drug discontinuation were related to hyperbilirubinemia

(e.g. jaundice, ocular icterus), and renal impairment. The bilirubin-related events are consistent with the known safety profile for ATV as described in labeling.

3.2.3 Other events of interest

3.2.3.1 Hepatic and Hepatobiliary events

In the pooled analysis, 461 hepatobiliary related AEs (of all causality and any severity) were reported in 298 (39%) subjects with comparable percentages of subjects in each treatment group (ATV/COBI 159 [40%], ATV/RTV 139 [37%]). The most commonly reported event was cholestasis and jaundice, which occurred in 97 ATV/COBI cases; 74 cases were jaundice and 43 cases were hyperbilirubinemia; as compared to 55 jaundice cases and 34 hyperbilirubinemia cases, respectively in the ATV/RTV group. There were 68 cases of ocular icterus reported in each ABT/COBI and ABT/RTV groups. There were only two hepatobiliary-related AEs in the pooled analysis that were serious in nature, one in each treatment group. In the ATV/COBI group, one Grade 2 event of increased hepatic enzyme on Study Day 71 was not considered related to the study drug. The other AE occurred in the ATV/RTV group, which consisted of a Grade 3 event of increased gamma glutamyltransferase (GGT). This event was attributed to the subject's underlying fatty change in the liver and their alcohol consumption. The GGT levels returned to baseline and the AE was considered resolved. There were no Grade 4 events.

AEs that occurred in the safety update period are either similar to events occurring with ritonavir-boosted ATV or ritonavir-boosted DRV, unlikely related to COBI, or consistent with proposed labeling with respect to hepatic monitoring, which is consistent with the prescribing information for ATV and DRV (since it will be co-administered with these drug products).

3.2.3.2 Renal Events

In the ATV/COBI + TVD group in the original NDA submission, there was 1 report of a Grade 3 SAE of acquired Fanconi Syndrome. In the safety update, there were additional reports of renal SAEs of interest (nephrolithiasis: n= 2, calculus ureteric: n= 2, renal colic: n=1, renal hematoma: n=1, acute renal failure: n= 1, decreased GFR: n=1, and various nephropathies: n=3). All events were either unlikely related to ATV/COBI, consistent with AEs occurring with ATV/RTV, or are consistent with the proposed COBI label as it pertains to events similar to those that occur with PIs.

3.2.4 Postmarketing Requirements

PMRs were sent to the Applicant in April 2013. There are no changes to the PMRs. PMRs include pediatric studies with ATV/COBI and DRV/COBI under the Pediatric Research Equity Act (PREA) and drug-drug interaction studies to evaluate the effects of ATV/COBI and DRV/COBI on oral contraceptives, rosuvastatin, and atorvastatin.

4 DISCUSSION

Based on the results of the phase 3 pivotal trial and phase 2 supportive trial, COBI provides efficacy in boosting the exposure of the HIV-1 protease inhibitors ATV and DRV. COBI, when compared with RTV, more selectively inhibits CYP3A; is a less potent inducer of other metabolizing enzymes in vitro, and it has been shown to have less potential for clinically

significant drug interactions via the non-CYP3A pathways. Additionally, COBI is a pharmacokinetic (PK) boosting agent and does not have any intrinsic HIV-1 antiretroviral activity; therefore, COBI does not increase the risk of resistance if used alone or due to non-compliance.

Overall, no new safety concerns were identified from the trials involving COBI during the update period after the original submission. The AEs observed in the trials are either consistent with proposed labeling as it pertains to protease inhibitor (PI)-boosted ARV regimens (similar to events occurring with ATV/RTV or DRV/RTV), or unlikely related to COBI.

COBI will be used as a PK booster similarly as RTV, which also has some ATV pharmacologic activity. RTV has been used to increase the exposures of other PIs for nearly a decade; thus, the drug interaction profile of RTV is generally well characterized. Because COBI is similar to RTV as a PI booster, the Applicant has voluntarily proposed an education plan (outside of a REMS) targeting HIV prescribers and pharmacists to highlight the unique aspects of the drug and to differentiate it from RTV (e.g., COBI is not interchangeable with RTV). The limitations of use and safety issues associated with COBI are clearly specified in the proposed labeling. Thus, it is our assessment that a REMS is not needed for this product.

The most likely prescribers of COBI are specialists who are familiar with the management of HIV patients and who understand the risks of treatment using antiretroviral therapies that have more serious risk profiles. Therefore, the risks of COBI may be adequately communicated by the Prescribing Information.

Therefore, DRISK does not recommend a REMS as necessary to ensure the benefits of COBI outweigh the risks.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for COBI. COBI has proven efficacy in boosting the exposure of the HIV-1 protease inhibitors ATV and DRV. There were no serious or severe safety issues which warrant a Boxed warning for COBI. Thus, the benefit-risk profile for COBI is acceptable and the risks can be adequately communicated through professional labeling.

Should DAVP have any concerns or questions, feel that a REMS may be warranted for this product, or new safety information becomes available, please send a consult to DRISK.

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09/11/2014

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