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APPLICATION NUMBER:

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SUMMARY REVIEW

Decisional Review for NDA 203094

Date	April 26, 2013
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 203094
Proprietary / Established (USAN) names	Tybost™ Cobicistat (Cobi)
Dosage forms / strength	Cobi 150 mg once daily coadministered with: Atazanavir 300 mg once daily Darunavir 800 mg once daily
Proposed Indication(s)	For use as a CYP 3A inhibitor to increase systemic exposures of atazanavir (ATV) and darunavir in the treatment of HIV-1 infection in adults
Action	Complete Response

1. **Introduction to Review:** This Division Director's memorandum provides an overview of NDA 203094 for Gilead Sciences' New Drug Application (NDA) for Tybost (Cobi), a CYP3A inhibitor for use only with atazanavir (ATV) in HIV-infected adults. This decisional review summarizes clinical trial results that provide support for the proposed indication; other pertinent findings from the multidisciplinary reviews will be highlighted. Requested post-marketing studies and product labeling are also summarized.

2. **Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Office of Scientific Investigations (OSI) Status/Other:** The NDA for Cobi was submitted on June 26, 2012, and received on June 28, 2012. Cobi is a CYP3A inhibitor to be used only with ATV 300 mg once daily. Cobi structurally resembles ritonavir, a protease inhibitor that is used as a CYP3A inhibitor at doses lower than its labeled indication for use in treatment of HIV-1 infected subjects.

   Cobi is a component of STRIBILD, a fixed-dose combination of four drugs – elvitegravir/Cobi/emtricitabine/tenofovir disoproxil fumarate for use as a single treatment regimen in treatment-naïve HIV-1 infected patients; STRIBILD was approved in August 2012. CMC, non-clinical and clinical data from the STRIBILD NDA were also used to support the Cobi NDA. Cobi will only be indicated for use with the protease inhibitor ATV based on results from the phase 1 Trial 110 that evaluated the relative bioavailability and pharmacokinetics of ATV when coadministered with Cobi versus ritonavir and from phase 2 Trial 105 and phase 3 Trial 114 that contained a PK subtrial. Phase 2 and 3 trials in treatment-naïve subjects evaluating ATV/Cobi compared to ATV/ritonavir each in combination with Truvada were reviewed and described in labeling. Three clinical trial sites from phase 3 Trial 114, two

domestic and one foreign were audited by the Office of Scientific Investigations (OSI). The trial sites were selected for review based on the numbers of patients enrolled per site. Per Dr. Antoine El-Hage, OSI, applicable statutory requirements and FDA regulations governing the conduct of clinical trials and the protection of human subjects were followed.

Although Cobi was also studied as a CYP3A inhibitor with darunavir (DRV), another protease inhibitor in Study 115, there is a lack of long-term stability data for DRV combined with Cobi in the same plasma matrix, per consultation with the Office of Scientific Investigations. Approximately 60 days of long-term stability data for DRV combined with Cobi in the same plasma matrix are needed. Since this data will not be submitted until late June 2013, DAVP administratively split NDA 203094 into two NDAS: Original NDA 1 for ATV/Cobi and Original NDA 2 for DRV/Cobi. Original NDA 2 for DRV/Cobi will receive a Complete Response for the bioanalytical issues cited above. (b) (4)

(b) (4)

The application was granted a 10-month standard review.

Importantly, Cobi drug interactions may not be the same as those with ritonavir. Consequently, Cobi labeling provides information regarding certain Cobi interactions that can not be extrapolated from ritonavir, including but not limited to warfarin, phenytoin, voriconazole, and oral contraceptives. Further, the Agency plans to perform outreach with healthcare providers and patients via a Medscape interview, updates on the HIV/AIDS list serves, and a stakeholder call to alert the public that Cobi is not interchangeable with ritonavir. The applicant, Gilead Sciences, will also disseminate a Dear Healthcare Provider letter.

3. **Chemistry/Manufacturing/Controls (CMC):** The CMC reviews of the Cobi NDA were conducted by Drs. Fuqiang Liu and Deepika Lakhani. Drs. Rapti Madurawe and Sandra Suarez supervised the CMC review with Dr. Stephen Miller serving as CMC-Lead. The CMC team could not recommend approval of the Cobi NDA at the time of completion of the CMC reviews due to the pending establishment evaluation. The Foster City site was subsequently inspected (b) (4). Some deficiencies identified during the inspection include, but are not limited to: 1) (b) (4) test methods for release of Cobi drug substance were not validated; 2) not all validation data for (b) (4) test methods for release and stability were available upon request; and 3) there were no validation reports for the release and stability test methods for the clinical and primary stability batches.

Specifically, under 21 CFR 314.125 (b)(13), parts 210 and 211, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with current good manufacturing practice regulations. Further, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability under 21 CFR 314.125 (b)(1). Thus, a withhold approval recommendation was made by the Office of Compliance. This forms the basis for the Complete Response regulatory decision.

4. **Pharmacology/Toxicology:** Most of the Cobi pharmacology and toxicology data have previously been reviewed under the STRIBILD NDA by Drs. Peyton Myers and Mark Powley with supervisory concurrence by Dr. Hanan Ghantous. Carcinogenicity studies in mice and rats were submitted with the original Cobi NDA. In the 2-year carcinogenicity study in mice, no drug-related increases in tumor incidence were observed at Cobi exposures 7-16X the human equivalent exposure at the therapeutic daily dose. In the 2-year carcinogenicity study in rats, increases in follicular cell adenomas and/or carcinomas of the thyroid gland were seen. These findings are considered species specific and secondary to hepatic microsomal enzyme induction. These liver enzyme induction-associated effects are not relevant for humans per the pharmacology/toxicology reviewers.

   Genotoxicity assays were also submitted in NDA 203094. Cobi was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay.

5. **Clinical Pharmacology:** The Office of Clinical Pharmacology reviewers were Drs. Stanley Au, Jeffry Florian and Shirley Seo.

   Cobi is structurally similar to ritonavir, an antiretroviral primarily used in practice to pharmacokinetically increase exposures of other protease inhibitors. Cobi, like ritonavir, is a CYP3A inhibitor. Cobi also inhibits the following transporters; p-glycoprotein, OATP1B1, OATP1B3, and BCRP. As such, caution must be used when administering Cobi with concomitant medications. It is also important to note that Cobi and ritonavir are not interchangeable because they have unique drug interaction profiles when coadministered with ATV. Labeling highlights the differences in the Warnings and Precautions and Drug Interactions sections. There is a separate subsection (b) (4) under the Warnings and Precautions section. For example, Cobi should not be used with more than one

antiretroviral agent that requires pharmacokinetic enhancement (i.e., two protease inhibitors or a protease inhibitor in combination with elvitegravir) because dosing recommendations for such combinations have not been established and may result in decreased plasma concentrations of the antiretroviral agents, leading to loss of therapeutic effect and development of resistance. Labeling includes the following wording:

Consideration should be given to evaluating whether dosing adjustments of concomitant medications or coadministered antiretrovirals drugs will need to be made in the following scenarios:

- **Patients on a stable concomitant medication who initiate or switch to a Cobi-containing regimen**
- **Patients on a Cobi-containing regimen who initiate a new concomitant medication**
- **Patients initiating a Cobi-containing regimen and a new concomitant medication simultaneously**

The pharmacokinetics of Cobi were also evaluated in special populations. In subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min) there were no clinically relevant differences in Cobi pharmacokinetic parameters between subjects with severe renal impairment compared to healthy subjects. In addition, the pharmacokinetics of Cobi were evaluated in subjects with moderate hepatic impairment (Child-Pugh Class B). Although Cobi is primarily metabolized and eliminated by the liver, there were no clinically relevant differences in Cobi pharmacokinetic parameters between subjects with moderate hepatic impairment and healthy subjects; no dose adjustment of Cobi is necessary for subjects with mild-to-moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh

Class C) on the pharmacokinetics of Cobi has not been studied and specific dosing recommendations are not available.

The following medications outlined in Table 2 in labeling are contraindicated with use of Cobi because of the potential for serious and life-threatening reactions or loss of therapeutic effects:

Table 1 Drugs That Are Contraindicated for TYBOST (cobicistat) Coadministered with ATV

Drug Class	Drugs within Class that are Contraindicated	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist	alfuzosin	Potential for increased alfuzosin concentrations, which can result in serious or life threatening reactions such as hypotension.
Antiarrhythmics	dronedarone	Potential for increased dronedarone concentrations.
Antimycobacterial	rifampin	Rifampin is a potent inducer of CYP metabolism and coadministration may cause a significant decrease in the plasma concentrations of atazanavir or darunavir and result in loss of therapeutic effect and development of resistance.
Antineoplastics	irinotecan	Atazanavir inhibits UGT1A1 and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicity.
Ergot Derivatives	dihydroergotamine, ergotamine, methylergonovine	Potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort (*Hypericum perforatum*)	Products containing St. John's wort may result in reduced plasma concentrations of atazanavir or darunavir, which may result in loss of therapeutic effect and development of resistance.
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.
Neuroleptic	pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Phosphodiesterase-5 (PDE5) Inhibitor	sildenafil[a] when dosed as REVATIO® for the treatment of pulmonary arterial hypertension	A safe and effective dose has not been established for coadministration of sildenafil (REVATIO®) when used for the treatment of pulmonary hypertension. There is increased potential for sildenafil-associated adverse events (which include visual disturbances, hypotension, priapism, and syncope).
Sedative/hypnotics	triazolam, orally administered midazolam[b]	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Co-administration of triazolam or orally administered midazolam may cause large increases in the concentration of these benzodiazepines. The potential exists for

		serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

a. See *Drug Interactions (7), Table 6* for sildenafil when dosed as VIAGRA for erectile dysfunction.

b. See *Drug Interactions (7), Table 6* for parenterally administered midazolam.

Mechanistically, Cobi has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. This effect needs to be considered when interpreting changes in estimated creatinine clearance in patients starting a Cobi-boosted regimen, particularly in patients with medical conditions or receiving drugs needing monitoring with estimated creatinine clearance. In labeling, dosing recommendations are not available for drugs that require dosing adjustment for renal impairment with use of Cobi. Health care providers are encouraged to consider alternative medications that do not require dosing adjustments.

When Cobi is used in combination with tenofovir disoproxil fumarate urine glucose, protein and creatinine clearance should be monitored because cases of acute renal failure and Fanconi syndrome have been described in the STRIBILD NDA. Serum phosphorus should also be monitored in patients with or at risk of renal impairment.

Dose-finding was adequate based on a multiple-dose relative bioavailability trial, 110, and the ATV/Cobi phase 2 (105) and 3 (114) trials. The recommended dose of Cobi is 150 mg once daily in combination with ATV 300 mg once daily to be taken with other antiretroviral drugs. Cobi and ATV should be taken together and with food based on ATV labeling recommendations.

The Applicant conducted a thorough QT study with Cobi that was submitted and reviewed under the STRIBILD NDA. FDA's QT Interdisciplinary Review Team concluded Cobi's effect on QTc prolongation was below 10 msec, the threshold for regulatory concern. Prolongation of the PR interval was noted in subjects receiving Cobi in the same study. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) msec for 250 mg dose and 20.2 (22.8) msec for the 400 mg Cobi dose. This information is included in section 12 of labeling.

6. **Clinical Virology:** Please see the review by Dr. Takashi Komatsu with supervisory concurrence by Dr. Jules O'Rear. No new nonclinical virology studies were submitted with the Cobi NDA. In the combined phase 2 and 3 clinical trial analysis, no subjects developed primary ATV resistance-associated substitutions. Of the 14 subjects who experienced virologic failure in the ATV/COBI arm there were 12 amino acid substitutions in the protease region (PR) compared to seven amino acid substitutions in the PR from seven subjects with virologic failure in the ATV/RTV arm. These substitutions are of unknown significance.

   Per the CDTL review by Dr. Kim Struble, in phase 3 trial (114), 12 subjects were considered virologic failures in the ATV/COBI group by Dr. Komatsu's analyses. Among the 12 subjects, 11 had evaluable genotypic data. Two of the 11 subjects developed the emtricitabine-associated resistance substitution M184V. No tenofovir-associated resistance was observed in these subjects. In comparison, genotypic data was available for all 12 virologic failures in the ATV/RTV arm and no subjects developed any resistance associated mutations to any component of their regimen.

7. **Efficacy and Safety:** Clinical and statistical reviews were conducted by Dr. Peter Miele and Dr. Yanming Yin. Dr. Kim Struble supervised the clinical review and Dr. Fraser Smith provided secondary statistical review. The intended use of Cobi is to increase the systemic exposures of ATV. This activity was shown in Trial 110 and in pharmacokinetics subtrials of the 105 and 114 trials. Phase 2 and 3 trials in treatment naïve subjects (105 and 114, respectively) were conducted to collect data on the actual use of Cobi when given with ATV as part of an antiretroviral regimen. In the pooled efficacy analyses, the percentage of subjects with HIV-1 RNA $\leq$ 50 copies /mL at week 48 was 85% in the ATV/Cobi arm compared to 87% in the ATV/ritonavir arm with a treatment difference of – 2.5% (95% CI -7.5, 2.4%) . The proportion of subjects with HIV RNA > 50 copies/mL at week 48 was 6% in the ATV/Cobi group and 5% in the ATV/ritonavir group. Reasons for virologic failure were balanced between groups.

   From a regulatory perspective, phase 2 and 3 clinical trials were not designed to establish the contribution of Cobi to an antiretroviral regimen compared to ritonavir. Rather, phase 2 and 3 trials supported the safety and tolerability along with effectiveness of an antiretroviral regimen comprised of ATV/Cobi with Truvada compared to ATV/ritonavir plus Truvada after it was determined that ATV exposures were similar when ATV was administered with either Cobi or ritonavir.

Issues have been raised as to whether the regimen containing Cobi was non-inferior (NI) to the regimen containing ritonavir in Trial 114. The original margin was set at (b) (4) partially for sample size purposes; this NI margin is for the regimen or a clinical margin, M2 as outlined in the Guidance for Industry for antiretroviral drugs using plasma HIV RNA measurements. In their review of NDA 203094, statistical reviewers stated that this was too wide for a non-inferiority determination to establish Cobi's contribution toward virologic response (via boosting of ATV) of the regimen and recommended a much smaller margin of (b) (4); this would be for a statistical margin, M1. The intent of Trial 114 was never to establish Cobi's contribution to a regimen because it does not have antiviral activity. Notably, this NDA is primarily based on trials demonstrating comparable exposures of ATV when administered with Cobi or ritonavir along with supportive data demonstrating relative effectiveness of one regimen compared to another from phase 2 and 3 clinical trials. Therefore, the lower bound of the 95% CI around the treatment difference in pooled Trials 105 and 114 is acceptable.

The safety assessment of Cobi is primarily based on pooled data from Trials 105 and 114 in which 394 subjects received ATV/Cobi and 377 subjects received ATV/ritonavir (n=377) both in combination with TRUVADA for at least 48 weeks. The most common adverse reactions (all Grades) and reported in >10% of subjects in the ATV/Cobi group were jaundice (13%) and nausea (12%); the most common adverse reactions in the ATV/ritonavir group were jaundice (11%), nausea (11%), and diarrhea (11%). The proportion of subjects who discontinued study treatment due to adverse events was comparable between groups. Table 3 in labeling displays the frequency of treatment-emergent adverse reactions (Grades 2-4) occurring in at least 2% of subjects receiving Cobi coadministered with ATV and TRUVADA in Trials 105 and 114.

Nephrolithiasis is a known adverse event related to ATV. In the pooled analysis of Trials 105 and 114 through 48 weeks, eight subjects (2%) receiving ATV/Cobi developed nephrolithiasis compared with none in the ritonavir group. Median time to onset of nephrolithiasis in the Cobi group was 24 weeks. The majority of renal stone events were not serious and no subject discontinued study drug. In the pooled analysis of Trials 105 and 114 through 96 weeks, the incidence of nephrolithiasis was comparable between groups.

The frequency of treatment-emergent laboratory abnormalities (Grades 3-4) occurring in at least 2% of subjects in the ATV/Cobi group in pooled Trials 105 and 114 is presented in Table 4 in labeling and appears below.

Table 4 Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Subjects in the ATV/Cobi in Studies 105 and 114 (Week 48 pooled analysis)

	Cobi Coadministered with ATV + TRUVADA	Ritonavir Coadministered with ATV + TRUVADA
Laboratory Parameter Abnormality	N=394	N=377
Total Bilirubin (> 2.5 × ULN)	65%	56%
Creatine Kinase (≥ 10.0 x ULN)	5%	6%
Serum Amylase (> 2.0 × ULN)	4%	2%
ALT (>5.0 x ULN)	3%	2%
AST (>5.0 x ULN)	3%	2%
GGT (>5.0 x ULN)	2%	1%
Urine Glucose (Glycosuria) (≥ 1000 mg/dL)	3%	1%
Urine RBC (Hematuria) (> 75 RBC/HPF)	3%	2%

For subjects with serum amylase > 1.5 x upper limit of normal, a lipase test was also performed. The frequency of increased lipase (Grades 3-4) occurring in the ATV/Cobi (N=44) and ATV/ritonavir groups (N=34) was 9% and 6%, respectively.

Increases in serum creatinine and decreases in estimated creatinine clearance occurred early in treatment with Cobi, after which they stabilized. The mean (± SD) change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.4 ± 15.2 mL/min in the Cobi group and -9.1 ± 14.7 mL/min in the ritonavir group.

Acute renal failure and Fanconi syndrome were reported in the STRIBILD NDA when Cobi was used in an antiretroviral regimen that contains tenofovir disoproxil fumarate. In the pooled analysis of Trials 105 and 114, six (1.5%) subjects treated with ATV/Cobi and TRUVADA and six (1.6%) subjects treated with ATV/ritonavir and TRUVADA discontinued study drug due to a renal adverse event. Five of the six subjects (1.3% overall) in the Cobi group had laboratory findings consistent with proximal renal tubulopathy compared to two of six subjects (0.5% overall) in the ritonavir group. None of the five subjects in the Cobi group had renal impairment at baseline based on an estimated creatinine clearance less than 70 mL/min. The laboratory findings in these five subjects with evidence of proximal tubulopathy improved but did not completely resolve in all subjects upon discontinuation of study medication. Renal replacement therapy was not required in any subject. These findings also include one case of Fanconi syndrome in each group in the pooled analysis.

The following wording appears in product labeling under Warnings and Precautions:

- [redacted] in patients who have an estimated creatinine clearance below 70 mL/min because dose adjustment of tenofovir DF is required below 50 mL/min and such dose adjustments have not been established for coadministration with TYBOST.
- Document urine glucose and urine protein at baseline and perform routine monitoring of estimated creatinine clearance, urine glucose, and urine protein during treatment when TYBOST is used with tenofovir DF.
- Measure serum phosphorus in patients with or at risk for renal impairment.

[redacted]

8. **Postmarketing Requirements (PMR):** The following PREA PMR will be requested to address the development of EVG for the pediatric population:

   Conduct a trial to evaluate pediatric pharmacokinetics, safety, and antiviral activity of once daily ATV/Cobi combined with a background regimen in HIV-1 treatment-experienced pediatric subjects from 3 months to less than 18 years of age. Initial evaluation of ATV/Cobi exposure must be performed to allow dose selection. Using the doses selected and agreed upon with FDA, conduct a longer-term pediatric safety and antiviral activity assessment of ATV/Cobi plus background regimen, assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

   Protocol Submission: [redacted]
   Study Completion:
   Final Report Submission:

   In addition a drug interaction study with a representative oral contraceptive will be required as will separate drug interaction studies with rosuvastatin and atorvastatin. The rationale for evaluating two different HMG-CoA reductase inhibitors is that different pathways are involved in the disposition of rosuvastatin and atorvastatin.

9. **Advisory Committee:** This NDA was not presented before the Antiviral Products Advisory Committee.

Conclusions and Recommendations: I am in agreement with the conclusions of the reviewers that the risk-benefit ratio favors approval of Cobi as a CYP3A inhibitor to be used with ATV as part of an antiretroviral regimen in HIV-1 infected adults pending satisfactory resolution of facility inspection deficiencies and product quality concerns regarding the release and stability data contained in this NDA. Based on the decision of the Office of Compliance to withhold a recommendation of approval, Original NDA 1 for ATV/Cobi will receive a complete response based on inspectional findings that cannot be corrected during this review cycle. Original NDA 2 for DRV/Cobi will also receive a complete response based on CMC inspection issues along with the bioanalytical inspection issues cited previously.

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