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APPLICATION NUMBER:

203100Orig1s000

SUMMARY REVIEW

Decisional Review for NDA 203100

Date	August 6, 2012
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 203100
Proprietary / Established (USAN) names	Stribild™ Elvitegravir/cobicistat/emtricitabine/tenofovir DF
Dosage forms / strength	150/150/200/300 mg in a fixed-dose combination tablet, once daily, with food
Proposed Indication(s)	For use as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve and who have no known substitutions associated with resistance to the individual components.
Action	Approval

- 1. Introduction to Review:** This Division Director's memorandum provides an overview of NDA 203100 for Gilead Sciences' New Drug Application (NDA) for Stribild for use as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve and who have no known amino acid substitutions associated with resistance to the individual components of this fixed-dose combination. This decisional review highlights clinical trial results that were used to support the safety and efficacy of this four-drug, single treatment regimen as well as other pertinent findings from the multidisciplinary reviews mostly as they pertain to the two new molecular entities; requested post-marketing studies and product labeling are also summarized.
- 2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Division of Scientific Investigations (DSI) Status:** The NDA for Stribild was submitted on October 27, 2011. Stribild is a fixed-dose combination (FDC) of four drugs including two new molecular entities, elvitegravir (EVG), an integrase strand transfer inhibitor (INSTI) and cobicistat (COBI), a pharmacoenhancer and two drugs already marketed, emtricitabine (FTC), a nucleoside reverse transcriptase inhibitor (NRTI) and tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor (N(t)RTI). The FDC is intended as a complete regimen. The application was granted a 10-month standard review because there are already multiple regimens available for naïve patients including one pill, once-a-day regimens.

Four clinical trial sites were audited by the Division of Scientific Investigations. The trial sites were selected for review based on the numbers of patients enrolled per site and site-specific protocol violations. Minor protocol violations were identified, however they were not considered serious enough to affect

data integrity. In sum, applicable statutory requirements and FDA regulations governing the conduct of clinical trials and the protection of human subjects were followed.

- 3. Chemistry/Manufacturing/Controls (CMC):** The CMC reviewers of the Stribild NDA are: Drs. Celia Cruz, Milton Sloan, and Fuqing Liu. Dr. Deepika Lakhani reviewed the biopharmaceutics portion of the CMC data. Drs. Stephen Miller and Rapti Madurawe supervised the CMC review. Stribild is a film-coated, immediate-release tablet containing four active ingredients: EVG, COBI, FTC and TDF. The manufacture of this product is complex. (b) (4)

Appropriate stability data was provided for Stribild tablets, including long-term data at both 25 degrees C/60% RH and 30 degrees C/75% RH.

The NDA also contains CMC information about the version of the tablet that will be used in resource poor settings. The "Access tablet" is identical to the tablet for US use except that it has a different color of the film coating and different debossing. For both tablets, stability data supported a shelf-life of 24 months when stored in the approved container at the agreed-upon labeled conditions (USP Controlled Room Temperature for the US tablet; Store below 30 degrees C for the Access tablet).

The Applicant provided adequate data to assure the identity, strength, purity and quality of the drug product, however according to the CMC team, this NDA could not be recommended for approval at the time of completion of the CMC review because inspections by the Office of Compliance identified deficiencies with the (b) (4) facility (b) (4). Gilead Sciences withdrew this manufacturing site on August 1, 2012. This action was acceptable to FDA reviewers (b) (4)

In addition pre-approval field inspections revealed further deficiencies at Gilead's facility in Foster City, California; these FDA 483 observations dated July 11, 2012, are outlined below:

- ❖ There is failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.
- ❖ The written stability testing program is not followed.
- ❖ Established laboratory control mechanisms are not followed.
- ❖ Laboratory records do not include complete data derived from all tests, examinations, and assays necessary to assure compliance with established specifications and standards. Specifically, review of chromatographic raw

data showed multiple discrepancies between results found in the Empower II software and results reported to the Agency in NDA 203100.

- ❖ Deviations from written test procedures are not recorded and justified. Specifically, there were multiple instances where chromatography samples were reanalyzed without written justification/documentation as required by standard operating procedures.
- ❖ Written procedures for sampling and testing plans are not followed for each drug product.
- ❖ Deviations from written production and process control procedures are not recorded.

Gilead Sciences submitted responses to these observations on July 30, 2012, and they are under review by the Office of Compliance at this time.

4. Pharmacology/Toxicology: See non-clinical reviews of EVG and COBI by Drs. Peyton Myers, Pritam Verma and Mark Powley with supervisory concurrence by Dr. Hanan Ghantous. Product labeling contains non-clinical data reviewed by our pharmacology/toxicology team. Their conclusions, as reflected in the product labeling are below. Also, non-clinical data on FTC and TDF have been previously reviewed and are not included in this memorandum.

Animal Data

***EVG:** Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures (AUC) at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 23 and 0.2 times higher than the exposure in humans at the recommended daily dose of 150 mg.*

***COBI:** Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures (AUC) at the embryo-fetal NOAELs in rats and rabbits were respectively 1.8 and 4.3 times higher than the exposure in humans at the recommended daily dose of 150 mg.*

Stribild is a pregnancy category B drug based on animal data as there are no adequate and well-controlled studies in pregnant women. The labeling states that healthcare providers are encouraged to register patients in the Antiretroviral Pregnancy Registry and monitor fetal outcomes of pregnant women exposed to Stribild. Further, because animal reproduction studies are not always predictive of human response, Stribild should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following wording related to EVG and COBI carcinogenicity, mutagenesis and fertility is included in product labeling:

EVG: Long-term carcinogenicity studies of were carried out in mice (104 weeks) and in rats for up to 88 weeks (males) and 90 weeks (females). No drug-related increases in tumor incidence were found. *EVG* was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an *in vitro* chromosomal aberration test, *EVG* was negative with metabolic activation; however, an equivocal response was observed without activation. *EVG* did not affect fertility in male and female rats at exposures approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at the therapeutic 150 mg daily dose.

COBI: The assessment of the carcinogenicity studies of cobicistat is ongoing as studies were not submitted with this original NDA submission. *COBI* was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays. *COBI* did not affect fertility in male or female rats at daily exposures (AUC) approximately 4-fold higher than human exposures at the recommended 150 mg daily dose.

- 5. Clinical Pharmacology:** Clinical pharmacology reviews were conducted by Drs. Vikram Arya, Stanley Au and Leslie Chinn. Pharmacometrics reviews were conducted by Dr. Jeffrey Florian and concurrence was provided by Dr. Yaning Wang. Dr. Kellie Reynolds supervised the clinical pharmacology and pharmacometrics reviews.

Under 21 CFR 300.50, two or more drugs may be combined in a single dosage form when each component makes a contribution and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling of the drug. *In vivo* data satisfy the regulations pertaining to the combination of drugs in *Stribild*. *Stribild* is a complete regimen containing a nucleos(t)ide backbone with a boosted integrase strand transfer inhibitor.

Stribild contains *COBI*, a pharmacokinetic enhancer that acts by inhibiting CYP3A enzymes. The role of *COBI* in *Stribild* is to increase the plasma concentrations of *EVG*. *COBI* also inhibits the enzyme CYP2D6 and transporters such as p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Coadministration of *Stribild* with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs. Of note, *EVG* is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates. Drugs that induce CYP3A can alter the concentrations of one or more components of *Stribild*. Importantly, refer to Table 1 below and product labeling for drugs that are contraindicated with use of *Stribild*.

To underscore the complexity of drug-drug interactions, when *Stribild* was studied in a drug-drug interaction study with an oral contraceptive containing

norgestimate and ethinyl estradiol, increases were seen in the concentration of the progestational component, norgestimate. The mean AUC_{τ} of norgestromin (NGMN; the pharmacologically active metabolite of norgestimate) increased by 126% and the mean AUC_{τ} of ethinyl estradiol decreased by 25%. Increases in norgestimate are associated with increased risks of insulin resistance, dyslipidemia, acne, and venous thrombosis. The potential risks and benefits associated with coadministration of norgestimate/ethinyl estradiol with Stribild should be considered, particularly in women who have risk factors for these events. Coadministration of Stribild with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestogens other than norgestimate has not been studied; therefore, alternative (non-hormonal) methods of contraception should be considered. Also see Table 5 in product labeling.

Coadministration of Stribild with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, TDF, and other renally eliminated drugs because FTC and TDF are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Some examples of drugs that are eliminated by active tubular secretion include acyclovir, cidofovir, valacyclovir, and valganciclovir.

Gilead Sciences will be requested to conduct drug-drug interaction trials of Stribild with telaprevir, methadone, and buprenorphine/naloxone to provide quantitative drug-drug interaction information for the safe and effective use of the combination in HIV-1 infected patients. Gilead Sciences will also be requested to conduct a pharmacokinetic (PK) subtrial of the renal safety trial in women to evaluate the potential for a drug-drug interaction between Stribild and commonly used oral contraceptives.

Exposure-response analyses focused on EVG (efficacy and safety) and COBI (safety). Exposure-response (efficacy) analyses were not performed for COBI because the primary role of COBI is to increase the systemic exposure of EVG and based on the available information, COBI does not have antiviral activity. Exposure-response safety analyses for EVG and COBI focused on adverse events of interest from the Phase 3 trials. Additional exposure-response safety analyses for COBI evaluated changes in renal function due to COBI exposure.

A relatively flat exposure-response efficacy relationship was identified across EVG exposures (EVG AUC_{τ} (min-max) was 4358-69754 ng·hr/mL; C_{τ} (min-max) was 58-2341 ng/mL). No significant covariates, such as baseline viral load, were identified as predictive of response across the EVG exposures. No exposure-response relationship was observed between predicted EVG AUC_{τ} or C_{τ} and adverse events of interest.

Likewise, similar COBI exposures (AUC_{τ} and C_{τ}) were observed between subjects with and without adverse events of interest. No relationship between

COBI AUC_{τ} and change in eGFR were observed based on the available COBI pharmacokinetic data.

For critical comments concerning exposure-response analysis, please see review by Dr. Jeffrey Florian.

The Applicant conducted separate, thorough QT studies with EVG and COBI. These studies were reviewed by the FDA's Interdisciplinary Review Team for QT Studies (IRT). The IRT concluded EVG's effect on QTc prolongation was below the threshold for regulatory concern and there appeared to be no clinically relevant effects on PR and QRS intervals. The COBI effect on QTc was also below the level of concern. See section 12.2 of product labeling for information related to effects on electrocardiograms.

Table 1: Drugs that are Contraindicated with STRIBILD

Drug Class	Drugs within class that are contraindicated with STRIBILD	Clinical Comment
Alpha 1-Adrenoreceptor Antagonist	Alfuzosin	Potential for increased alfuzosin concentrations, which can result in hypotension.
Antimycobacterial	Rifampin	Rifampin is a potent inducer of CYP450 metabolism. STRIBILD should not be used in combination with rifampin, as this may cause significant decrease in the plasma concentration of elvitegravir and cobicistat. This may result in loss of therapeutic effect to STRIBILD.
Ergot Derivatives	Dihydroergotamine Ergotamine Methylethylergonovine	Potential for serious and/or life-threatening events 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 events such as cardiac arrhythmias.
Herbal Products	St. John's wort (Hypericum perforatum)	Patients taking STRIBILD should not use products containing St. John's wort because co-administration may result in reduced plasma concentrations of elvitegravir and cobicistat. This 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 events 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 in combination with STRIBILD has not been established for 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 with STRIBILD may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

- a. See Drug Interactions (7), Table 5 for sildenafil when dosed as VIAGRA[®] for erectile dysfunction.
- b. See Drug Interactions (7), Table 5 for parenterally administered midazolam

6. Clinical Virology: Please see extensive reviews by Drs. Sung Rhee and Takashi Komatsu with supervisory concurrence by Dr. Jules O'Rear.

Resistance and cross-resistance were evaluated in treatment-naïve patients using virus samples from Stribild-treatment failure subjects in principal Studies 102 and 103 who were viremic with HIV-1 RNA greater than 400 copies per mL at virologic failure, at Week 48, or at the time of early study drug discontinuation. Genotypic and phenotypic data are available for 23 subjects [3%, 23/669]. The following description appears in product labeling:

The development of one or more primary substitutions associated with resistance to EVG, FTC, and/or TDF was observed in 57% (13/23) of the viremic subjects with evaluable genotypic data. The most common substitutions that emerged were M184V/I (N=12) in HIV-1 RT and the primary elvitegravir resistance-associated substitutions T66I (N=2), E92Q (N=8), Q148R (N=3), and N155H (N=3) in integrase; K65R in RT was also detected (N=4). In isolates with primary EVG resistance substitutions, additional substitutions in integrase associated with resistance to EVG were H51Y, L68I/V, G140C, S153A, E157Q, V165I, and H183P.

Importantly, most subjects (N=10) who developed integrase substitutions associated with EVG resistance also developed the M184I/V RT substitutions, conferring reduced susceptibility to both EVG and FTC.

Cross resistance within the INSTI and NRTI drug classes was observed. These isolates, however, remained susceptible to other drug classes including NNRTIs and protease inhibitors. The following wording appears in product labeling:

EVG: Cross-resistance has been observed among INSTIs. EVG-resistant viruses showed varying degrees of cross-resistance in cell culture to raltegravir depending on the type and number of substitutions in HIV-1 integrase. Among the four primary EVG resistance-associated substitutions detected in the Stribild-treatment virologic failure isolates, E92Q, Q148R, and N155H individually conferred reduced susceptibility both to EVG (greater than 32-fold) and raltegravir (greater than 5-fold) when introduced into a wild-type virus by site-directed mutagenesis. The T66I substitution conferred greater than 14-fold reduced susceptibility to EVG but less than 3-fold to raltegravir. Among the three primary raltegravir resistance-associated substitutions (Y143H/R, Q148H/K/R, and N155H), all but one (Y143H) conferred significant reductions in susceptibility to EVG (greater than 5-fold).

COBI is structurally similar to the HIV-1 protease inhibitor ritonavir. Possible protease inhibitory activity was assessed by comparing the protease sequences in failure isolates from the Stribild and Atripla[®] (ATR) treatment

arms of Trial 102. A greater number of substitutions in the protease sequence developed on treatment in the Stribild treatment arm (9 substitutions/14 subjects) compared to the control arm (4 substitutions/15 subjects). Notably, three of the nine protease substitutions in isolates from the Stribild arm have been associated with resistance to protease inhibitors (M36I, D60E, and V77I), however they are not considered primary resistance substitutions. As the clinical relevance of this observation is unclear at this time, Gilead Sciences will be conducting additional analyses.

- 7. Efficacy and Safety:** Clinical and statistical reviews were conducted by Drs. Adam Sherwat and Wen Zeng, respectively. Dr. Linda Lewis supervised the clinical review and Dr. Fraser Smith provided secondary statistical review. The two principal phase 3 trials were 102 and 103 and they provided the primary safety and efficacy data to support the labeled indication. Both trials were multicentered, randomized, double-blind, double-dummy studies designed to assess the safety and efficacy of Stribild. The two studies were identical in design except for the active control. The active control for Trial 102 was ATR, while Trial 103 utilized ritonavir-boosted atazanavir (ATV/r) plus Truvada® (TVD) as the active control. In addition, phase 2 Trial 104 provided supportive data.

In Trial 102, patients were randomized in a 1:1 ratio to receive either Stribild (N=348) once daily or ATR (N=352) once daily. The mean age was 38 years (range 18-67), 89% were male, 63% were White, 28% were Black, and 2% were Asian. Twenty-four percent of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.8 log₁₀ copies per mL (range 2.6–6.5). The mean baseline CD4+ cell count was 386 cells per mm³ (range 3-1348) and 13% had CD4+ cell counts less than 200 cells per mm³. Thirty-three percent of subjects had baseline viral loads greater than 100,000 copies per mL.

In Trial 103, patients were randomized in a 1:1 ratio to receive either Stribild (N=353) once daily or atazanavir 300 mg + ritonavir 100 mg (ATV+RTV) + TVD (N=355) once daily. The mean age was the same as in Trial 102 and only 10% of patients were female, similar to Trial 102. Compared to Trial 102, the mean baseline plasma HIV-1 RNA was the same and the mean baseline CD4+ cell count was 370 cells per mm³ (range 5-1132) with 13% having CD4+ cell count less than 200 cells per mm³. Forty-one percent of subjects had baseline viral loads greater than 100,000 copies per mL.

In both studies, subjects were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies per mL or greater than 100,000 copies per mL).

Treatment outcomes of Trials 102 and 103 through 48 weeks are presented below and in Table 9 as it appears in product labeling.

Virologic Outcome of Randomized Treatment of Trials 102 and 103 Week 48

	Trial 102		Trial 103	
	STRIBILD (N=348)	ATRIPLA (N=352)	STRIBILD (N=353)	ATV + RTV + TVD (N=355)
Virologic Success HIV-1 RNA < 50 copies/mL	88%	84%	90%	87%
Treatment Difference	3.6% (95% CI = -1.6%, 8.8%)		3.0% (95% CI = -1.9%, 7.8%)	
Virologic Failure^b	7%	7%	5%	5%
No Virologic Data at Week 48 Window				
Discontinued Study Drug Due to AE or Death ^c	3%	5%	3%	5%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^d	2%	3%	2%	3%
Missing Data During Window but on Study Drug	0%	<1%	0%	<1%

- a. Week 48 window is between Day 309 and 378 (inclusive).
- b. Includes subjects who had ≥ 50 copies/mL in the Week 48 window, subjects who discontinued early due to lack or loss of efficacy, subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
- c. Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
- d. Includes subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

In the two pivotal Phase 3 trials, Stribild was non-inferior to the comparator groups. In Trial 102, 87.6% of patients receiving Stribild had virologic success compared to 84.1% in the ATR group. In Trial 103, 89.5% of patients receiving Stribild had virologic success compared to 86.8% of subjects in the boosted ATV group. Rates of virologic failure were low in the Stribild groups and similar to rates demonstrated in the comparator groups.

Regarding safety, the package insert already has a boxed warning regarding lactic acidosis and post-treatment exacerbation of hepatitis B, similar to what is in TVD's package insert.

The primary safety comparison is between EVG/COBI and either efavirenz or ATV/r because all treatment arms contained FTC/TDF. The safety profile of FTC/TDF is well-characterized in multiple previous clinical trials and is notable for TDF-associated renal toxicity related to proximal renal tubule dysfunction and bone toxicity related to loss of bone mineral density and evidence of increased bone turnover.

The safety assessment of Stribild is based on pooled data from 1408 subjects in two comparative clinical trials 102 and 103. A total of 701 subjects received Stribild once daily for at least 48 weeks.

The proportion of subjects who discontinued treatment with Stribild, ATR or boosted ATV + TVD due to adverse events, regardless of severity ranged from 3.7%, to 5.1%. See Table 2 in product labeling that displays the frequency of adverse drug reactions greater than or equal to 5%. The frequency of treatment-emergent laboratory abnormalities (Grade 3-4) occurring in at least 2% of subjects receiving Stribild in Trials 102 and 103 are presented in Table 3 in product labeling and comprise four categories: AST, amylase, creatine kinase and hematuria.

Laboratory Abnormalities (Grades 3-4) Reported in \geq 2% of Patients Receiving STRIBILD in Trials 102 and 103 at Week 48

	STRIBILD	ATR	ATV/r + TDV
Laboratory Parameter Abnormality	N=701	N=352	N=355
AST (>5.0 x ULN)	2%	3%	4%
Amylase ^a (>2.0 x ULN)	2%	2%	4%
Creatine Kinase (\geq 10.0 x ULN)	5%	11%	7%
Urine RBC (Hematuria) (> 75 RBC/HPF)	3%	1%	2%

a. For subjects with serum amylase > 1.5 x upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grade 3-4) occurring in STRIBILD (N=58), ATRIPLA (N=33), and atazanavir + ritonavir + TRUVADA (N=33) was 12%, 15%, and 21%, respectively.

In section 5.3 of product labeling, renal impairment is highlighted. The label specifically states that renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF and with the use of Stribild.

In the clinical trials of STRIBILD over 48 weeks (N=701), 8 (1.1%) subjects in the STRIBILD group and 1 (0.1%) subject in the combined comparator groups discontinued study drug due to a renal adverse event. Four (0.6%) of the subjects who received STRIBILD developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of STRIBILD compared to none in the comparator groups. Two of these four subjects had renal impairment (i.e. estimated creatinine clearance less than 70 mL per min) at baseline. The laboratory findings in these 4 subjects with evidence of proximal tubulopathy improved but did not completely resolve in all subjects upon discontinuation of STRIBILD.

Based on the review of the data it is recommended that estimated creatinine clearance, urine glucose and urine protein should be documented in all patients prior to initiating therapy and that Stribild should not be initiated in patients with estimated creatinine clearance below 70 mL per min. Further, it is recommended

to routinely monitor estimated creatinine clearance, urine glucose, and urine protein during Stribild therapy in all patients; serum phosphorus should also be measured in patients at risk for renal impairment. The label also recommends that patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety.

8. Postmarketing Requirements (PMR):

The following PREA PMRs will be requested to address the development of Stribild for the pediatric population:

Pediatric:

- 1. Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 12 to <18 years of age. Include in the trial safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).**

Protocol Submission: September 2012

Study Completion: March 2016

Study Report Submission: November 2016

- 2. Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 6 to <12 years of age. Dose selection must be based on pharmacokinetic data for individual component drugs and discussed with FDA prior to initiation of trial. Include in the trial safety monitoring assessment of potential renal toxicity (serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).**

Protocol Submission: October 2017

Study Completion: May 2021

Study Report Submission: August 2021

The following PMRs have been established to better characterize the incidence of and risk factors for renal toxicity in women taking Stribild, additional drug interactions, and resistance-associated substitutions in viral isolates from subjects failing therapy with Stribild:

Clinical:

- 3. Perform a clinical trial to better characterize the incidence of and risk factors for renal adverse events in women. Provide adequate renal monitoring in the proposed trial to assess renal safety employing a renal monitoring algorithm similar to that used in GS-US-236-0102 and GS-US-236-0103. The algorithm will include an assessment of serum creatinine, creatinine clearance by Cockcroft-Gault, glomerular filtration rate (GFR) by cystatin C, serum phosphate, fractional excretion of phosphate, urine protein and urine glucose. The trial will enroll approximately 500 women, in order to assess the relative incidence of and risk factors for renal adverse events in women as compared to men enrolled in other Stribild clinical trials.**

Protocol Submission: October 2012

Study Completion: July 2016

Study Report Submission: November 2016

Clinical Pharmacology:

- 4. Conduct a pharmacokinetic (PK) subtrial of the renal safety trial in women to evaluate the potential for a drug-drug interaction between Stribild and commonly used oral contraceptives. Intensive pharmacokinetic data on each oral contraceptive, when given alone and when co-administered with Stribild, should be collected in an adequate number of subjects.**

Protocol Submission: October 2012

Study Completion: July 2016

Study Report Submission: November 2016

5. Conduct an *in vivo* drug-drug interaction trial between Stribild and telaprevir.

Protocol Submission: November 2012
Study Completion: September 2013
Study Report Submission: October 2013

6. Conduct an *in vivo* drug-drug interaction trial of Stribild and buprenorphine/naloxone.

Protocol Submission: January 2011
Study Completion: September 2012
Study Report Submission: January 2013

7. Conduct an *in vivo* drug-drug interaction trial of Stribild and methadone.

Protocol Submission: January 2011
Study Completion: September 2012
Study Report Submission: January 2013

Clinical Virology

8. Assess possible COBI protease inhibitory activity *in vivo* by sequencing the protease in virologic failure subjects' isolates from Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0121, GS-US-236-0123 and GS-US-236-0128.

Protocol Submission: December 2012
Study Completion: October 2016
Study Report Submission: February 2017

In addition the Applicant will be assessing what impact COBI has on intracellular tenofovir concentrations and the mechanism of any observed interaction.

9. Advisory Committee

This NDA was presented before the Antiviral Products Advisory Committee on May 11, 2012. Following presentations and discussion, advisory committee members were asked to vote on the following question related to the risk-benefit of Stribild. The specific voting question and results follow:

VOTE: Considering the overall risks and benefits, do the available data support approval of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate as a complete regimen for treatment of HIV-1 infection in treatment-naïve adults?

YES: 13 NO: 1 ABSTAIN: 0

Conclusions and Recommendations: NDA203100 was a unique new drug application because it contained data on two new chemical entities that had not been previously approved. This presented a challenge from a safety perspective as it was more difficult to understand the safety profile of the individual components of the FDC. Nonetheless, it appears that the combination of COBI with TDF may have more renal toxicity than TDF alone as highlighted in the clinical reviews and the renal consult. However, with careful monitoring as recommended by the clinical review team and advisory committee members and recommendations presented in product labeling, it seems that renal function can be monitored and managed to avoid serious toxicity. Gilead Sciences will be conducting a large trial in women to further assess safety including renal toxicity and additional studies to assess whether known TDF renal toxicity is enhanced by coadministration of COBI.

At present, there are a multitude of available antiretroviral therapies in six classes. In addition there are fixed-dose combinations (FDC) that provide a full treatment regimen in a single formulation. The availability of FDCs can serve to facilitate adherence to a treatment regimen which is extremely important for HIV-1 treatment so as to reduce the risk of development of resistant virus. Stribild provides another choice of an FDC in the armamentarium of antiretrovirals for treatment of HIV-1.

In sum, based on the review of the data contained in this NDA and the conclusions of the multidisciplinary review team I am in agreement that the risk-benefit ratio favors approval of Stribild for treatment naïve adults who are HIV positive. However, I can not state my full support for approval until all CMC/facility manufacturing issues are resolved to the satisfaction of the Office of Compliance.

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/s/

DEBRA B BIRNKRANT
08/06/2012