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APPLICATION NUMBER:

203100Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	NDA 203100
Applicant Name	Gilead Sciences, Inc.
Date of Submission	October 27, 2011
PDUFA Goal Date	August 27, 2012
Proprietary Name / **Established (USAN) Name**	Stribild elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
Dosage Forms / Strength	Fixed dose combination tablet containing elvitegravir 150 mg cobicistat 150 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg
Proposed Indication(s)	for the treatment of HIV-1 infection in adults who are treatment-naïve
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Adam Sherwat
Statistical Review	Wen Zeng, Fraser Smith
Pharmacology Toxicology Reviews	Pritam Verma, L. Peyton Myers, Mark Powley, Min Min, Karl Lin, Hanan Ghantous, Abby Jacobs
CMC Review/OBP Reviews	Celia Cruz, Milton Sloan, Fuqiang Liu, Deepika Lakhani
Clinical Virology	Sung Rhee, Takashi Komatsu
IRT Consult	Nitin Mehrotra, Monica Fiszman, Norman Stockbridge
Cardio-Renal Consult	Shona Pendse, Norman Stockbridge
DRUP Consult	Gerald Willet, Lisa Soule, Audrey Gassman
Clinical Pharmacology Review	Vikram Arya, Stanley Au, Leslie Chin, Jeffry Florian, Yaning Wang, Kellie Reynolds
OSI	Antoine El-Hage, Susan Liebenhaut, Susan Thompson
OSE/DMEPA	Morgan Walker, Jamie Wilkins, Carol Holquist
CDTL Review	Linda Lewis
Division Director's Review	Debbie Birnkrant

OND=Office of New Drugs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Stribild is a fixed dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. Elvitegravir is an HIV-1 integrase inhibitor and cobicistat is a pharmacoenhancer that increases exposure to elvitegravir. These two previously unapproved active ingredients are combined with two previously approved HIV-1 nucleoside reverse transcriptase inhibitors, emtricitabine and tenofovir disoproxil fumarate. Stribild was studied as a one pill, once a day regimen for treatment of HIV in treatment-naïve patients.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of Stribild. For a detailed discussion of NDA 203100, the reader is referred to the individual discipline specific reviews. In addition Dr. Lewis's Cross-Discipline Team Leader Review and Dr. Birnkrant's Division Director Review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

The Office of New Drug Quality Assessment recommends approval of Stribild. The ONDQA reviewers find that the information in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support a 24-month shelf life for the commercial product when it is stored at controlled room temperature. As of August 21, 2012, the manufacturing facilities have been found to be in compliance with cGMPs.

The recommendation from the pharmacology/toxicology reviewer is for approval. Stribild is labeled as Pregnancy Category B reflecting that there have not been studies in pregnant women and no significant embryo/fetal toxicity was observed in animal studies.

The Clinical Virology Review included an evaluation of the mutations associated with resistance to elvitegravir. Mutations identified associated with reduced susceptibility to elvitegravir are described in the product labeling. Labeling also describes subjects who developed integrase substitutions associated with elvitegravir resistance also developed the M184I/V reverse transcriptase substitutions, conferring reduced susceptibility to both elvitegravir and emtricitabine.

The Clinical Pharmacology reviewer finds the data in the application acceptable. The Clinical Pharmacology Reviews note that elvitegravir exposure is increased when taken with food. Hence, labeling recommends taking Stribild with food. Elvitegravir is principally metabolized by CYP3A4. Cobicistat is metabolized by CYP3A4 and CYP2D6 and is also a CYP3A4 inhibitor. Cobicistat's primary role as a component of Stribild is to inhibit the metabolism of elvitegravir in order to increase exposure of elvitegravir to targeted levels.

No dose adjustment of Stribild is required in the setting of mild hepatic impairment. Stribild has not been studied in persons with severe hepatic impairment. Emtricitabine and tenofovir disoproxil fumarate are renally eliminated; Stribild should not be continued in persons with creatinine clearance less than 50 mL/min as proper dose adjustment in the setting of renal compromise cannot be achieved with Stribild, a fixed dose combination tablet. In addition, the labeling also noted that Stribild should not be initiated in persons with creatinine clearance less than 70 mL/min. The labeling also described steps for monitoring renal function while on Stribild.

The labeling provides information on drug interactions with Stribild, and additional drug interaction studies will be required as postmarketing studies. The effect of elvitegravir and separately for cobicistat were evaluated in thorough QT studies and found to be below the threshold of regulatory concern by the Interdisciplinary Review Team for QT studies (IRT).

In support of the evaluation of Stribild for the treatment of HIV in treatment-naïve patients, the applicant performed two randomized phase 3 trials that compared Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) to Atripla (efavirenz/ emtricitabine/tenofovir disoproxil fumarate) in Study 102 and to atazanavir boosted with ritonavir plus emtricitabine/tenofovir disoproxil fumarate in Study 103. The primary efficacy endpoint in the trials was the proportion of subjects achieving HIV-1 RNA < 50 copies/mL at 48 weeks. The studies were designed as non-inferiority (NI) studies with an NI margin (M2) of 12%. The basis for the NI margin is described in the Statistical Review. The primary efficacy endpoint was met in each of the two studies, demonstrating the efficacy of Stribild.

The safety database from the phase 3 trials included 701 patients treated with Stribild. The product labeling notes the potential for renal toxicity and loss of bone mineral density. These effects have been observed with emtricitabine and tenofovir disoproxil fumarate. Also of note in the safety analysis was that cobicistat inhibits tubular secretion of creatinine, resulting in modest increases in serum creatinine in the absence of an effect on glomerular filtration. In addition to the effect on creatinine secretion, in the clinical trials there were more serious renal adverse events in the Stribild arms potentially reflecting that cobicistat may exacerbate the known renal adverse effects of tenofovir disoproxil fumarate. The product labeling states that patients should have an estimated creatinine clearance, a test for urine glucose and a test for urine protein documented before starting Stribild and the same should be monitored while on therapy. Stribild should not be initiated in patients with a creatinine clearance less than 70 mL/min.

Included in the product labeling is a boxed warning on lactic acidosis that is included in labeling for nucleos(t)ide analogues and a warning about post-treatment acute flares of hepatitis B (and that Stribild is not approved for the treatment of chronic hepatitis B) that is included in the emtricitabine and tenofovir disoproxil fumarate labeling. The product labeling also includes a patient package insert that provides information about Stribild.

The application for Stribild was presented to the Antiviral Drugs Advisory Committee (AVDAC) on May 11, 2012. The Committee discussed the efficacy findings and the safety of Stribild, including the renal adverse effects of Stribild observed in the clinical trials. The AVDAC voted, 13 Yes; 1 No, recommending approval of Stribild based on the benefits outweighing the risks. The Committee also recommended that the labeling provide information on the renal adverse effects and patient management.

With regard to the Pediatric Research Equity Act (PREA), the pediatric study requirement for this application is being waived for children less than 6 years of age because in this age range proper dose adjustment cannot be achieved with the component drugs in this fixed dose combination. Pediatric studies for children for ages 6 to less than 18 years of age have been deferred and the approval includes required pediatric studies to be completed in this age group.

The approval also includes required postmarket studies to further evaluate renal adverse effects in women, mechanisms of renal effects, additional drug-drug interaction studies and studies to evaluate resistance.

In summary, I agree with the review team that the overall benefits and risks support the approval of NDA 203100. The product labeling adequately describes the safety and efficacy findings. Postmarketing studies will provide additional information to evaluate selected safety issues and pediatric safety and efficacy.

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Edward Cox, MD, MPH
Director, Office of Antimicrobial Products
OND/CDER/FDA

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/s/

EDWARD M COX
08/27/2012