2.2 INTRODUCTION

ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/
TENOFOVIR ALAFENAMIDE
FIXED DOSE COMBINATION

(E/C/F/TAF FDC)

NDA 207561

Gilead Sciences, Inc.

[redacted] **20**[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

BMD	bone mineral density
CAS	chemical abstract service
COBI, C	cobicistat
COBI on silicon dioxide	cobicistat on silicon dioxide (GS-9350), drug substance
CYP3A	cytochrome P450 3A
DAVP	Division of Antiviral Products
DNA	deoxyribonucleic acid
E/C/F/TAF	elvigtegravir/cobicistat/emtricitabine/tenofovir alafenamide
EVG, E	elvitegravir (GS-9137; JTK-303), drug substance
EVG/COBI/FTC/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC, F	emtricitabine (GS-9019), drug substance
FTC/TDF	emtricitabine/tenofovir DF, Truvada®
FTC-TP	emtricitabine 5'-triphosphate
HIV-1	human immunodeficiency virus type 1
IND	investigational new drug application
INSTI	integrase strand transfer inhibitor
IUPAC	International Union of Pure and Applied Chemistry
mg	milligram
NDA	new drug application
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
TAF	tenofovir alafenamide (GS-7340)
TAF fumarate	tenofovir alafenamide fumarate (GS-7340-03), drug substance
TDF	tenofovir DF, Viread®
TFV	tenofovir, PMPA
TFV-DP	tenofovir diphosphate
TVD	Truvada
US	United States
USAN	United States Adopted Name

1. INTRODUCTION

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF, Viread®), an oral prodrug of TFV, is a preferred nucleotide reverse transcriptase inhibitory (NtRTI) for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. While TDF is used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs {26885}. Tenofovir alafenamide (TAF) is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF.

Gilead Sciences, Inc (Gilead) has coformulated TAF fumarate with the HIV-1 integrase strand-transfer inhibitor (INSTI) elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C) on silicon dioxide, and the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC; F) into a fixed-dose combination (FDC) tablet that is suitable for once-daily use. The E/C/F/TAF FDC provides a potent, convenient, well-tolerated, and practical regimen for the long-term treatment of patients infected with HIV.

The clinical development plan for the E/C/F/TAF FDC tablet was discussed at the [redacted] meeting held on [redacted] 20[redacted]. At this meeting, Gilead discussed with the Division of Antiviral Products (DAVP) a proposal to advance the E/C/F/TAF FDC for the treatment of HIV-1 infection in adults and adolescents, and agreements were reached on the study design of pivotal clinical trials necessary to support the E/C/F/TAF FDC New Drug Application (NDA). Additionally, IND 111007 for E/C/F/TAF was granted Fast Track designation on [redacted] 20[redacted] ([redacted]).

Gilead requested a [redacted] meeting with the Agency on [redacted] 20[redacted] to discuss [redacted]. The comments received [redacted] were comprehensive; therefore, a request to cancel the [redacted] meeting was made on [redacted] 20[redacted], and a response to the Agency's [redacted] comments was submitted on [redacted] 20[redacted].

On [redacted] 20[redacted], a [redacted] meeting request was submitted, as requested by the Agency [redacted]. [redacted] meeting comments were received on [redacted] 20[redacted] therefore, a request to cancel the [redacted] meeting was made on [redacted] 20[redacted].

As TAF fumarate is a new chemical entity, the nonclinical and clinical summaries describe all available data on this component. Per the agreement reached between Gilead and the Food and Drug Administration (FDA;), this NDA is supported by [redacted].

FTC and TDF, as well as EVG and COBI as components of STB, are listed as preferred agents in United States (US) and International HIV treatment guidelines {29697}, {29584}, {28776}. These products are currently approved in the US, the European Community, and other countries worldwide for use in adults. In the US, FTC and TDF are also approved for use in children and adolescents. Additionally, in the US, FTC is approved as an oral solution formulation and may be administered to newborn children, and TDF is approved as an oral powder formulation that may be administered to pediatric patients 2 years of age and older for the treatment of HIV-1 infection.

The FDC is referred to as elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) throughout the summary documents. Each E/C/F/TAF FDC tablet contains TAF 10 mg and EVG, COBI, and FTC at the same dosages as in Stribild (i.e., 150 mg of EVG, 150 mg of COBI, and 200 mg of FTC).

1.1. Chemical Name and Structures

Elvitegravir

USAN Name: Elvitegravir

Gilead Product No: GS-9137

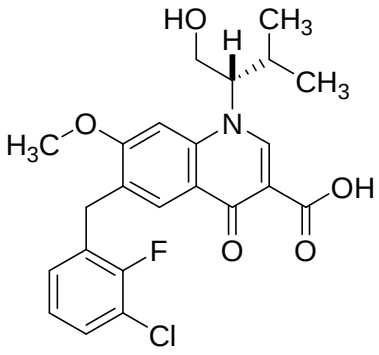
CAS Name: 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

IUPAC Name: 3-Quinolinecarboxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-

Empirical Formula: $C_{23}H_{23}ClFNO_5$

Molecular Weight: 447.88 g/mol

Chemical Structure:



Cobicistat

USAN Name: Cobicistat

Gilead Product No: GS-9350

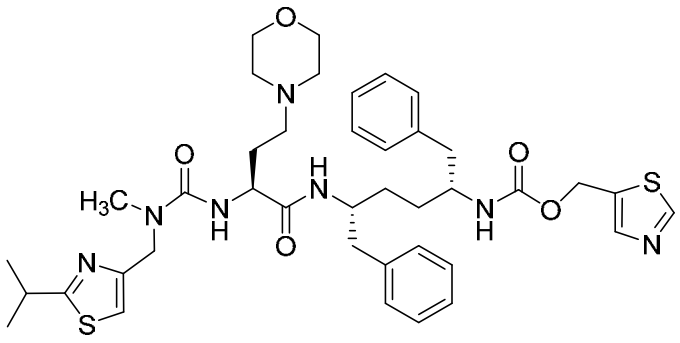
CAS Name: 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl), 5-thiazolylmethyl ester, (3*R*,6*R*,9*S*)

IUPAC Name: 1,3-Thiazol-5-ylmethyl (2*R*,5*R*)-(5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]]-4-(morpholin-4-yl)butanamido}-1,6-diphenylhexan-2-yl)carbamate

Empirical Formula: $C_{40}H_{53}N_7O_5S_2$

Molecular Weight: 776.0 g/mol

Chemical Structure:



Emtricitabine

USAN Name: Emtricitabine

Gilead Product No: GS-9019

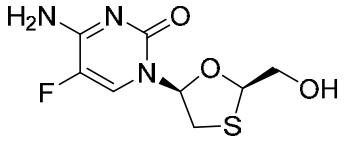
CAS Name: 4-Amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one

IUPAC Name: 5-Fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.24 g/mol

Chemical Structure:



Tenofovir Alafenamide

USAN Name: Tenofovir alafenamide fumarate

Gilead Product No: GS-7340-03

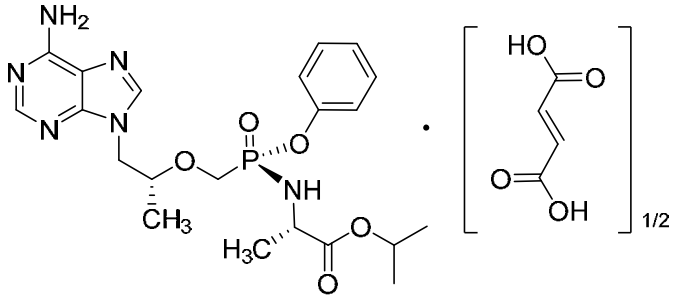
CAS Name: *L*-Alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1)

IUPAC Name Propan-2-yl *N*-[(*S*)-({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate, (2*E*)-but-2-enedioate (2:1)

Empirical Formula: $C_{23}H_{31}O_7N_6P$

Molecular Weight: 534.50 g/mol

Chemical Structure:



1.2. Pharmacological Class

Elvitegravir

Elvitegravir is an HIV-1 INSTI that inhibits the HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus. The provirus is required for production of progeny virus, so inhibiting integration prevents propagation of the viral infection.

Cobicistat

Cobicistat is a selective mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily (primarily CYP3A4 and CYP3A5). Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as EVG, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism. Cobicistat on silicon dioxide (nominally 50 wt%) is the drug substance.

Emtricitabine

Emtricitabine is a NRTI, and is a synthetic analog of the naturally occurring pyrimidine nucleoside, 2′-deoxycytidine. Intracellularly, FTC is phosphorylated enzymatically to form emtricitabine triphosphate (FTC-TP), the active metabolite. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination.

Tenofovir Alafenamide

Tenofovir alafenamide, an oral prodrug, is an NtRTI with a unique metabolism that provides enhanced lymphatic delivery of tenofovir (TFV), resulting in higher intracellular levels of the active phosphorylated metabolite, tenofovir-diphosphate (TFV-DP), and lower circulating levels of TFV as compared with TDF. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5’-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir alafenamide fumarate is the drug substance.

1.3. Route of Administration

E/C/F/TAF is administered orally, once daily, with food.

1.4. Proposed Indication

[E/C/F/TAF TRADENAME] is indicated for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

Limitations of Use:

[E/C/F/TAF TRADENAME] is not recommended for use in patients with any known mutations associated with resistance to the individual components of [E/C/F/TAF TRADENAME].

1.5. References

26885 Gilead Sciences Inc. VIREAD® (tenofovir disoproxil fumarate) tablets, for oral use VIREAD® (tenofovir disoproxil fumarate) powder, for oral use. U.S. Prescribing Information. Foster City, CA. Revised October 2013. 2013:

28776 Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). Revised 01 May 2014. Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. 2014.

29584 European AIDS Clinical Society (EACS). European Treatment Guidelines Version 7.02. June, 2014.

29697 Huldrych F, Gunthard HF, Aberg JA, Eron JJ, Hoy JF, Telenti A, et al. Antiretroviral Treatment of Adult HIV Infection: 2014 Recommendations of the International Antiviral Society-USA Panel. JAMA 2014;312 (4):410-25.