SECTION 2.2 INTRODUCTION

EMTRICITABINE/TENOFOVIR ALAFENAMIDE FIXED DOSE COMBINATION

(F/TAF FDC)

NDA 208215

Gilead Sciences, Inc.

[redacted] **20**[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.2 INTRODUCTION 1
TABLE OF CONTENTS 2
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 3
1. INTRODUCTION 4
1.1. Chemical Name and Structures 6
1.2. Pharmacological Class 7
1.3. Route of Administration 8
1.4. Proposed Indication 8
1.5. References 9

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
BMD	bone mineral density
CAS	chemical abstract service
COBI	cobicistat
DNA	deoxyribonucleic acid
E/C/F/TAF	elvigtegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvigtegravir/cobicistat/emtricitabine/tenofovir DF
EFV	efavirenz
EVG	elvitegravir
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
OATP	organic anion transporting polypeptide
STB	Stribild®, elvigtegravir/cobicistat/emtricitabine/tenofovir DF
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

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide {27071}. Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression.

The success of potent and well-tolerated ART means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS–associated comorbidities. Clinical attention has become more focused on optimizing tolerability, long-term safety, and adherence {29705}.There remains a significant medical need for safe and effective new therapies that take into consideration the aging patient population, non-HIV–related comorbidities, virologic resistance, and regimen simplification.

For ART-naive HIV-infected patients, treatment guidelines recommend that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI). Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {32519}, {27621}.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is a prodrug of TFV. 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}, {34210}.

TDF in combination with emtricitabine (FTC; F) forms a guideline-recommended N(t)RTI backbone for ART-naive HIV-infected patients that can be combined with different third agents. The combination of FTC and TDF is used within several once-daily fixed-dose combinations (FDCs) (Truvada® [TVD; FTC/TDF], Atripla® [ATR; efavirenz (EFV)/FTC/TDF], Complera®/Eviplera® [FTC/rilpivirine/TDF], and Stribild® [STB; elvitegravir (EVG; E)/cobicistat (COBI; C)/FTC/TDF]). Availability of a stand-alone NRTI backbone is important when there is a medical need to use a third agent that is not part of an FDC (eg, ritonavir [RTV]-boosted PIs), and particularly to provide a range of treatment options in patients with virologic resistance to their third agent but not to the backbone.

Tenofovir alafenamide (TAF) is an investigational prodrug of TFV. TAF is more stable in plasma than TDF. In HIV target cells including lymphocytes and macrophages, TAF provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP). Additionally, circulating levels of TFV are > 90% lower relative to TDF. The distinct metabolism of TAF offers an improved clinical profile compared with TDF.

Gilead Sciences (Gilead) has coformulated TAF (as TAF fumarate) with FTC into an FDC tablet available in 2 dosage strengths, F/TAF (200/25 mg) and F/TAF (200/10 mg). Because, TAF is a substrate of intestinal efflux transporters (ie, P-glycoprotein [P-gp]) and hepatic transporters

(ie, organic anion transporting polypeptide [OATP]1B1 and OATP1B3), TAF exposure may be increased upon coadministration with inhibitors of these transporters, with the effect driven predominantly by P-gp inhibition (ie, by RTV or COBI; m2.7.2, Sections 3.1.3.4 and 3.2.3.2.2). Therefore, the recommended F/TAF dose (200/25 mg or 200/10 mg based on third agent) is generally based on whether or not the coadministered agent has any clinically relevant effect on TAF exposure (eg, via inhibition of intestinal P-gp). Specifically, F/TAF 200/25 mg is recommended to be used with unboosted third agents, and F/TAF 200/10 mg with boosted third agents.

This submission for the N(t)RTI backbone F/TAF is based on 2 pivotal bioequivalence studies (Studies GS-US-311-1472 and GS-US-311-1473) that pharmacokinetically bridge each F/TAF FDC tablet strength (200/25 mg and 200/10 mg) to Gilead's FDC tablet containing the HIV-1 INSTI EVG, the pharmacoenhancer COBI, FTC, and TAF (E/C/F/TAF 150/150/200/10 mg), for which clinical safety and efficacy have been established in a broad range of patient populations. This development plan was devised in consultation with the Agency in response to questions presented in a [redacted] Meeting briefing package on [redacted] 20[redacted], and a teleconference with the Agency on [redacted] 20[redacted] ([redacted]).

Per the agreement reached between Gilead and the Food and Drug Administration ([redacted]), this NDA is supported by [redacted]

1.1. Chemical Name and Structures

Emtricitabine

USAN Name: Emtricitabine

Gilead Product No: GS-9019

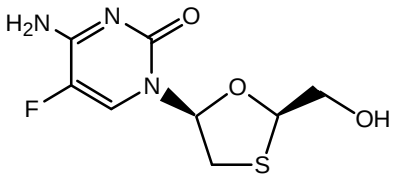
CAS Name: 4-Amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one

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

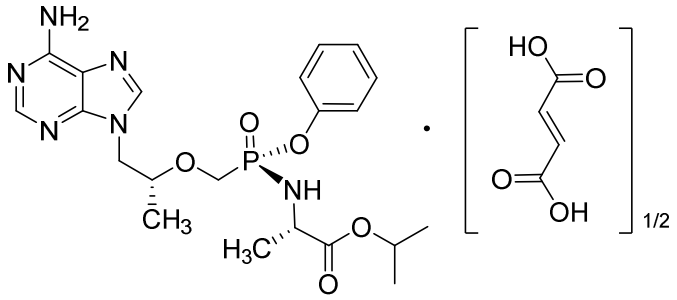
Chemical Structure:



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)
Alternate IUPAC name	9-{(R)-2-[((S)- {[(*S*)-1-(Isopropoxycarbonyl)ethyl]amino}-phenoxyphosphinyl)methoxy]propyl}adenine, fumarate (2:1)
Empirical Formula:	$C_{23}H_{31}O_7N_6P$
Molecular Weight:	534.5 g/mol

Chemical Structure:



1.2. Pharmacological Class

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, a prodrug, is an NtRTI with a unique metabolism that provides enhanced delivery of tenofovir (TFV) to lymphocytes and macrophages, 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

F/TAF is administered orally, once daily, without regard to food.

1.4. Proposed Indication

[F/TAF TRADENAME] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children 12 years of age and older.

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:

27071 Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic. 2013.

27621 Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). HIV Med 2014;15 Suppl 1:1-85.

29705 Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

32519 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). Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revised 13 November 2014.

34210 Gilead Sciences International Limited. Viread 245 mg film-coated tablets: Summary of Product Characteristics. United Kingdom. Updated December 2014. 2014: