SECTION 2.2 INTRODUCTION

EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE FIXED DOSE COMBINATION

(FTC/RPV/TAF FDC)

Gilead Sciences

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CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ARV	anti-retroviral
COBI	cobicistat
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
EVG/COBI/FTC/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil, Stribild®
EVG	elvitegravir
EU	European Union
FDC	fixed-dose combination
FTC, F	emtricitabine
FTC/RPV/TAF	emtricitabine/rilpivirine/tenofovir alafenamide
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil, Eviplera®
FTC/TDF	emtricitabine/tenofovir DF, Truvada®
HIV-1	human immunodeficiency virus type 1
INSTI	integrase strand transfer inhibitor
MAA	marketing authorisation application
NDA	new drug application
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
RPV, R	rilpivirine
TAF	tenofovir alafenamide
TAF fumarate	Tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate, Viread®
TFV	tenofovir, PMPA

1. INTRODUCTION

This Marketing Authorization Application (MAA) is for a fixed dose combination (FDC) tablet containing the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC; F), the nonnucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV; R as rilpivirine hydrochloride) and new active substance and nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir alafenamide (TAF as TAF fumarate): collectively referred to as the FTC/RPV/TAF FDC tablet. The FTC/RPV/TAF FDC is indicated for the treatment of adults and adolescents aged 12 years and older weighing at least 35 kg infected with human immunodeficiency virus 1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.

Emtricitabine is approved in the European Union (EU) as Emtriva® 200 mg hard capsules and 10 mg/mL oral solution for use in combination with other anti-retroviral (ARV) agents for the treatment of HIV-1 infection in adults and children aged 4 months and over (EU/1/03/261/001-003). FTC is also a component of Eviplera® (FTC/RPV/TDF) (EU/1/11/737/001-002), Stribild® (EVG/COBI/FTC/TDF) (EU/1/13/830/001-002) and Truvada® (FTC/TDF) (EU/1/04/305/001-002).

Rilpivirine, a diarylpyrimidine derivative, is a potent NNRTI with in vitro activity against wild type HIV-1 and NNRTI-resistant mutants. RPV was granted approval in the EU in November 2011 (EU/1/11/736/001) to Janssen-Cilag International NV under the tradename Edurant® and is indicated in combination with other ARV agents, for the treatment of HIV-1 infection in ARV treatment-naive adult patients with HIV-1 ribonucleic acid (RNA) ≤ 100,000 copies/mL at the start of therapy. RPV is also a component of Eviplera® (FTC/RPV/TDF) and is approved in the EU for the treatment of adults infected with HIV-1 without known mutations associated with resistance to the NNRTI class, TDF or FTC, and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), a prodrug of TFV, is a preferred NtRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. TDF is the active substance in Viread® and an active substance in the FDC products Truvada®,Atripla®,Eviplera®,and Stribild®,all approved in the EU via the centralized procedure for the treatment of HIV-1 infection. While these TDF-containing products are use broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk of TDF therapy, which also is associated with reductions in bone mineral density that are larger than those observed with other NRTIs used in ARV regimens {26885}.

TAF is an investigational oral prodrug of TFV that is more stable in plasma than TDF. TAF achieves higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP) and > 90% lower circulating levels of TFV relative to TDF. TAF has demonstrated an improved bone and renal safety profile compared with TDF in clinical studies, which is attributed to lower plasma TFV exposures compared to the approved dose of TDF.

Gilead has coformulated TAF with FTC and RPV into an FDC tablet, FTC/RPV/TAF (200/25/25 mg). This submission for FTC/RPV/TAF is based on a pivotal bioequivalence study (GS-US-366-1159) that demonstrated the following:

- Bioequivalence of TAF and FTC exposures between the FTC/RPV/TAF FDC (200/25/25 mg) and 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), thereby supporting extrapolation of the demonstrated safety and efficacy of TAF and FTC exposures in the FTC/RPV/TAF FDC to those from E/C/F/TAF.

- Bioequivalence of RPV exposure between the FTC/RPV/TAF FDC tablet and the marketed product Edurant (RPV 25 mg tablet), thereby supporting extrapolation of the demonstrated safety and efficacy of RPV exposures in the FTC/RPV/TAF FDC to those from Edurant®.

In accordance with the bioequivalence approach outlined above, the clinical efficacy and safety of E/C/F/TAF and RPV-containing regimens support the efficacy and safety of FTC/RPV/TAF in a broad range of populations.

The MAA for FTC/RPV/TAF FDC tablets is submitted as a 'standalone' application in accordance with the particulars set out in Directive 2001/83/EC, Article 8(3), as amended. Therefore, as agreed with the EMA, all studies to support the FTC/RPV/TAF FDC tablet application are included in the MAA with no cross-referencing to data previously submitted. These comprise all pharmaceutical chemical and pharmaceutical manufacturing and controls data, nonclinical tests, and clinical trials utilizing TAF, either alone or in combination with EVG, COBI, and/or FTC; as well as results from FTC and RPV nonclinical tests; results from FTC and RPV pivotal clinical trials; and other clinical studies necessary to support the proposed Product Information.

An overview of the quality of TAF drug substance and the FTC/RPV/TAF FDC tablet is provided in module 2.3. Quality summaries for FTC and RPV drug substances are consistent with the detail already presented in other commercially available drug products.

A comprehensive nonclinical pharmacology/virology, pharmacokinetic, and toxicology program was conducted to support the registration of FTC/RPV/TAF FDC. Information from nonclinical studies with FTC, RPV, TAF, TDF or TFV should be considered in the context of their clinical data and post marketing clinical experience within ARV combination therapy for the treatment of HIV-1 infection. This information with a review of the data is presented in module 2.4.

The clinical rationale for the development of FTC/RPV/TAF and a review of all data relevant to the benefit/risk assessment of the FTC/RPV/TAF FDC tablet in the treatment of HIV-1 infection is presented in module 2.5.

2. 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: