



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tenofovir disoproxil fumarate/emtricitabine/rilpivirine

Proprietary Product Name: Eviplera

Sponsor: Gilead Sciences Pty Ltd

March 2012

TGA Health Safety
Regulation

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	23 January 2012
<i>Active ingredient(s):</i>	Tenofovir disoproxil fumarate 300 mg Emtricitabine 200 mg Rilpivirine (as HCl) 25 mg
<i>Product Name(s):</i>	Eviplera
<i>Sponsor's Name and Address:</i>	Gilead Sciences Pty Ltd 128 Jolimont Rd, East Melbourne VIC 3002.
<i>Dose form(s):</i>	Tablet
<i>Strength(s):</i>	See Active Ingredient above
<i>Container(s):</i>	High density polyethylene (HDPE) bottle
<i>Pack size(s):</i>	30 tablets
<i>Approved Therapeutic use:</i>	Eviplera is indicated for the treatment of HIV infection in treatment-naïve adult patients with plasma HIV-1 RNA \leq 100,000 copies/mL at the start of therapy.
<i>Route(s) of administration:</i>	Oral (PO)
<i>Dosage:</i>	One tablet daily to be taken with a meal
<i>ARTG Number (s)</i>	176537

Product Background

Gilead Sciences Pty Ltd has registered in Australia various single agent or combination oral products containing tenofovir disoproxil fumarate (tenofovir DF, TDF) and/or emtricitabine (FTC). Viread tablets and Emtriva capsules are single active ingredient medicines, containing 300 mg tenofovir DF and 200 mg emtricitabine, respectively. Truvada tablets are fixed dose combination tablets containing 300 mg tenofovir DF and 200 mg emtricitabine. A triple combination tablet (Atripla) containing 300 mg tenofovir DF, 200 mg emtricitabine and 600 mg efavirenz is also registered.

Emtricitabine, a Nucleoside Reverse Transcriptase Inhibitor (NRTI), is a synthetic analogue of the naturally occurring nucleotide 2' deoxycytidine, a pyrimidine nucleoside, which is structurally similar to lamivudine (3TC). The active metabolite emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral deoxyribonucleic acid (DNA) which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α , β , ϵ and mitochondrial DNA polymerase γ . The primary route of elimination of FTC is renal excretion.

Rilpivirine (RPV) is a diarylpyrimidine Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). It binds directly to reverse

transcriptase and blocks the ribonucleic acid (RNA) dependent and DNA dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Human DNA polymerases α , β and γ are not inhibited by RPV. RPV primarily undergoes oxidative metabolism by the cytochrome P450 (CYP3A) system in the liver. Renal elimination of RPV is minimal.

Tenofovir disoproxil fumarate, the oral pro drug of tenofovir, is an N(t)RTI. Following absorption, TDF is rapidly converted to tenofovir, which is metabolised intracellularly to the active metabolite, tenofovir diphosphate. Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxyadenosine triphosphate) and after incorporation into DNA by DNA chain termination. Tenofovir diphosphate is a very weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ . The primary route of elimination of TDF is renal excretion by a combination of glomerular filtration and active tubular secretion.

Currently TDF and FTC are registered in Australia for the treatment of HIV-1 infection in single and fixed dose combination forms:

- Viread® (TDF 300mg): registered in August 2002 for use in combination with other antiretroviral drugs (ARV) drugs for the treatment of HIV-infected adults and paediatric patients 12 years of age and older. Also indicated for the treatment of chronic hepatitis B in adults.
- Emtriva® (FTC 200mg): registered in January 2005 for use in combination with other ARV drugs for the treatment of HIV-infected adults.
- Truvada® (TDF 300mg + FTC 200mg): registered in September 2005 for use in combination with other ARV drugs for the treatment of HIV-infected adults.
- Atripla® (TDF 300mg + FTC 200mg + EFV 600mg): Registered in August 2009 for the treatment of HIV infected adults.

Since successful therapy depends on a high level of adherence, once daily dosing regimens that incorporate fixed dose combination formulations are often preferred.¹ The proposed doses of the individual components of the combination are the same as those recommended for the individual drugs. Atripla (TDF/FTC/EFV) is the only multiclass fixed dose combination regimen available in Australia.

This AusPAR describes the application by Gilead's to register a new fixed dose combination tablet containing 300 mg tenofovir disoproxil fumarate, 200 mg emtricitabine and 25 mg rilpivirine (as the hydrochloride salt) for the treatment of HIV infection. This application is based on a single bioavailability study. A nonclinical evaluation has also been prepared.

Janssen-Cilag Pty Ltd has also recently applied to register rilpivirine (RPV) 25 mg tablets for the treatment of HIV infection. The rilpivirine and the Eviplera submissions were concurrently under evaluation by the TGA and Janssen-Cilag authorised cross reference to the rilpivirine submission in the evaluation of Gilead's application for Eviplera. The application for rilpivirine will be before the TGA's Advisory Committee on Prescription Medicines (ACPM) at the same time as the Eviplera triple agent fixed combination application.

¹ Antibiotic Expert Group. Therapeutic guidelines: antibiotic. Version 14. Melbourne: Therapeutic Guidelines Ltd; 2010.

Regulatory Status

The proposed combination of emtricitabine, tenofovir DF and rilpivirine was approved by the FDA on August 10, 2011 under the tradename Complera®. Emtricitabine (Emtriva®, AUST R 96426, 96427, nucleoside analogue) and tenofovir DF (Viread®, AUST R 90370, nucleotide analogue), and the fixed double combination of emtricitabine/tenofovir DF (300/200 mg, Truvada®, AUST R 107072) are currently registered in Australia, the US, European Union (EU) and other countries for treatment of HIV-1 infection in adults.

The following two tables (Tables 1 and 2) summarise the international regulatory status of this product.

Table 1. International Regulatory Status

Country	Status	Approval Date
USA	Approved	10 August 2011
Canada	Approved	23 September 2011
Europe	Approved	28 November 2011

Table 2. Approved indications

Country	Approved indication
USA	COMPLERA, a combination of 2 nucleoside analog HIV-1 reverse transcriptase inhibitors (emtricitabine and tenofovir disoproxil fumarate) and 1 non-nucleoside reverse transcriptase inhibitor (rilpivirine), is indicated for use as a complete regimen for the treatment of HIV-1 infection in treatment-naïve adults.
Canada	COMPLERA (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) is indicated for use alone as a complete regimen for the treatment of HIV-1 infection in antiretroviral treatment-naïve adults.
Europe	EVIPLERA is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load \leq 100,000 HIV-1 RNA copies/ml.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The drug substances are identical to those used in the currently registered products and rilpivirine tablets. Emtricitabine and tenofovir disoproxil fumarate are highly soluble in aqueous media while rilpivirine is practically insoluble.

Drug Product

The product has been formulated using commonly used excipients that comply with the standards defined in current US Pharmacopoeia (USP)/ National Formulary (NF) and European Pharmacopoeia (Ph. Eur.) monographs.

The routine quality control dissolution method applied to the tablets is based on that proposed for rilpivirine tablets.

Two new degradants of emtricitabine have been observed in Eviplera tablets. The limits proposed have been referred to the TGA's Medicines Toxicology Evaluation (Nonclinical) Section for assessment.

A shelf life of 2 years below 25°C has been satisfactorily established for Eviplera tablets.

Bioavailability

Two formulations (F3 & F4) of tenofovir DF/emtricitabine/rilpivirine tablets were compared in a single dose bioequivalence study with the three single agent products given concomitantly (Study GS-US-264-0103). As food is known to increase the bioavailability of both tenofovir DF and rilpivirine, the study was conducted under fed conditions.

The two test formulations were bioequivalent to the three single agent products with regard to tenofovir DF and emtricitabine but gave higher mean area under the plasma concentration time curve (AUC) and maximum plasma concentration (C_{max}) results with regard to rilpivirine. For both F3 and F4, the 90% confidence intervals (CI) for rilpivirine AUC were within 80-125%, although they did not encompass 100%. The same was true for C_{max} for F3. However, the 90% CI for the F4 C_{max} was not within the range 80-125%. On this basis, the sponsor concluded that F3 is bioequivalent to the three single agent tablets but F4 is not bioequivalent with regard to rilpivirine. F3 was therefore chosen as the formulation to be registered. The results are shown in tables 3 and 4 below.

Table 3. Analyte: Emtricitabine

	T_{max} (h)	C_{max} (%CV) (ng/mL)	AUC _t (%CV) (ng·h/mL)	AUC _∞ (%CV) (ng·h/mL)
Treatment				
A: FTC+RPV+TDF reference	2.00 (2.00-2.50)	1652.2 (21.9)	9417.5 (13.9)	9644.5 (13.6)
B: FTC/RPV/TDF Formulation 3	2.50 (2.00-3.00)	1753.9 (23.6)	9416.5 (14.3)	9636.3 (14.1)
C: FTC/RPV/TDF Formulation 4	2.50 (2.00-3.50)	1809.5 (28.6)	9494.1 (14.3)	9705.2 (13.9)
Statistical analysis:		ratio (%)	ratio (%)	ratio (%)
B vs. A Estimate		105.47%	99.94%	99.86%
90% CI		100.5-110.7%	97.8-102.2%	97.7-102.1%
C vs. A Estimate		107.90%	100.71%	100.5%
90% CI		102.8-113.3%	98.5-103.0%	98.3-102.8%

Table 4. Analyte: Rilpivirine

	T_{max} (h)	C_{max} (%CV) (ng/mL)	AUC_t (%CV) (ng·h/mL)	AUC_∞ (%CV) (ng·h/mL)
<i>Treatment</i>				
A: FTC+RPV+TDF reference	4.5 (4.0-4.5)	99.8 (30.5)	2597.2 (32.5)	2923.3 (38.6)
B: FTC/RPV/TDF Formulation 3	4.5 (4.0-4.5)	115.5 (29.6)	3014.4 (34.5)	3389.3 (39.4)
C: FTC/RPV/TDF Formulation 4	4.5 (4.0-4.5)	122.7 (32.4)	3037.4 (32.4)	3422.7 (38.1)
<i>Statistical analysis:</i>		<i>Ratio (%)</i>	<i>Ratio (%)</i>	<i>Ratio (%)</i>
B vs. A Estimate		115.9%	115.7%	115.6%
90% CI		108.2-124.1%	109.1-122.7%	108.7-123.0%
C vs. A Estimate		121.633%	117.1%	117.3%
90% CI		113.6-130.2%	110.5-124.2%	110.2-124.7%

Table 5. Analyte: Tenofovir

	T_{max} (h)	C_{max} (%CV) (ng/mL)	AUC_t (%CV) (ng·h/mL)	AUC_∞ (%CV) (ng·h/mL)
<i>Treatment</i>				
A: FTC+RPV+TDF reference	1.5 (1.0-2.0)	291.1 (26.4)	3040.3 (21.3)	3246.8 (19.7)
B: FTC/RPV/TDF Formulation 3	2.0 (2.0-2.5)	324.7 (26.0)	3108.2 (21.1)	3313.6 (19.7)
C: FTC/RPV/TDF Formulation 4	2.3 (1.5-2.5)	334.1 (26.4)	3177.7 (21.3)	3392.7 (19.6)
<i>Statistical analysis:</i>		<i>Ratio (%)</i>	<i>Ratio (%)</i>	<i>Ratio (%)</i>
B vs. A Estimate		111.0%	102.1%	102.0%
90% CI		104.2-118.3%	99.0-105.4%	99.1-105.0%
C vs. A Estimate		113.8%	104.1%	104.1%
90% CI		106.8-121.3%	100.9-107.4%	101.2-107.2%

Two earlier formulations of tenofovir disoproxil fumarate (TDF) / rilpivirine (RPV)/emtricitabine (FTC) tablets showed even higher bioavailability of rilpivirine relative to the single agent tablet given concomitantly with TDF and FTC; formulations 1 and 2 gave a 50% greater C_{max} and a 35% greater AUC for rilpivirine. The significantly higher bioavailability of rilpivirine in these formulations suggests that the rilpivirine single agent tablet is not optimally formulated. This has necessitated the development of a triple combination tablet that is also sub optimally formulated with respect to rilpivirine. This was considered a concern because a sub optimally formulated product may display

inconsistent bioavailability from batch to batch. This has been brought to the attention of the Clinical Delegate.²

The Delegate has also been advised that no information was provided on pharmacokinetic interactions amongst the three active ingredients and no relevant information is provided in the proposed draft PI.

Quality Summary and Conclusions

Except for deficiencies in the product labels and in the draft PI, there was no objection to registration of Eviplera tablets in respect of Chemistry, Manufacturing and Controls.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

- The sponsor submitted three in vitro studies in acutely infected MT-2 cells³, which demonstrated synergistic anti HIV-1 activity with the proposed combination. Resistance selection experiments yielded breakthrough mutations M184I after 22 days at 1.7 times the 50% effective concentration (EC₅₀) values for emtricitabine + rilpivirine + tenofovir, and K65R after 49 days at 3.3 times the EC₅₀. No further Reverse Transcriptase (RT) mutations were detected with higher multiples of the EC₅₀ values. Results of a cross resistance study indicate that HIV-1 strains with rilpivirine-associated mutations show a lack of cross resistance to emtricitabine and tenofovir.
- The oral exposure to emtricitabine, tenofovir and rilpivirine tablets administered to fasted beagle dogs as the current individual clinical tablet forms was comparable to that of all three active ingredients formulated together in a single bilayer tablet.
- Adequate justification was provided for the lack of nonclinical toxicity studies with the fixed triple combination, which was consistent with the TGA adopted European Union (EU) guideline on the Nonclinical Development of Fixed Combinations of Medicinal Products⁴ and was based on the nonclinical safety profiles for each of these compounds, the substantial clinical experience with emtricitabine and tenofovir in antiretroviral combination therapy for the treatment of HIV-1 infection, and on Phase II and Phase III clinical experience with rilpivirine, including in combination with Truvada®.
- The sponsor has provided updated specifications providing limits for the newly identified emtricitabine impurities. These impurities were present in a degraded preparation of emtricitabine and tenofovir, which was administered to rats as part of a 14 day repeat dose toxicity study previously evaluated by the TGA. Based on the No Observable Adverse Effect level (NOAEL) for the impurities in this study, the exposure to all three impurities (on the basis of weight per unit of body surface area) was

² The sponsor provided a response to the evaluator's comments during evaluation advising that the formulation of Eviplera selected for commercialisation achieved bioequivalence as assessed by C_{max}, AUC_{last}, and AUC_{inf}. The sponsor stated that the attributes of the formulation that contributed to the bioequivalence with the single-agent tablets were identified and are well controlled during manufacture. The sponsor also stated that the Eviplera formulation and manufacturing process has been demonstrated to be robust through process validation and testing of the process has been routinely performed during manufacture to demonstrate consistency from batch to batch.

³ The MT-2 cell culture assay is used to detect Syncytium inducing (SI) variants of HIV. The MT-2 cells are an Human T-lymphotropic virus Type I (HTLV-1) immortalized T-cell line. HTLV-1 is a human RNA retrovirus that is known to cause a type of cancer, referred to as adult T-cell leukemia.

⁴ EMEA/CHMP/SWP/ 258498/2005 at <http://www.tga.gov.au/pdf/euguide/swp25849805final.pdf>

approximately nine times the anticipated human exposure. It is therefore considered that the two impurities have been adequately qualified.

- It is noted that the supplementary information on the impurities refers to an application to the FDA based on toxicological qualification of these impurities.
- The impurities have not been qualified in genotoxicity studies, as recommended by the TGA adopted EU guideline for impurities in new drug products⁵ at levels above the qualification threshold. An in silico screen was negative, but this is not considered to be an acceptable surrogate for in vitro screening. However, the lack of genotoxicity data with the degradants is probably acceptable based on a similarity in structure with the parent compound and the need for adequate therapies for a life threatening condition.
- In vitro studies demonstrated synergistic anti HIV activity of the triple drug combination.
- The sponsor has provided adequate justification for the lack of nonclinical toxicity studies with the triple combination.
- Two recently identified emtricitabine degradants were adequately tested in a 2 week toxicity study with negative results. A minimum genotoxicity screen has not been conducted with either degradant; however the potential risk may be acceptable on clinical grounds for treatment of a life threatening condition.

IV. Clinical Findings

A separate clinical report has not been prepared as the application is cross referenced to a concurrent application for registration of a new NNRTI, rilpivirine, which will be before the ACPM at the same time as this triple agent fixed combination.

V. Pharmacovigilance Findings

Risk Management Plan (RMP)

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The sponsor has identified a number of Ongoing Safety Concerns relating to the fixed dose combination (FDC) product and the individual active agent components. These are summarised in Table 6 below.

⁵ CPMP/ICH/2738/99 ICH topic Q3B (R2): Note for Guidance on Impurities in New Drug products. <http://www.tga.gov.au/pdf/euguide/ich273799en.pdf>

Table 6. (a) Rilpivirine (RPV)

Important identified risks	Nil
Important potential risks	<ul style="list-style-type: none"> · QT prolongation · Hepatotoxicity · Severe skin reactions · Depression · Development of drug resistance
Important missing information	<ul style="list-style-type: none"> · Safety in children · Safety in elderly patients · Safety in pregnancy · Safety in lactation · Safety in patients with severe hepatic impairment (Child-Pugh score C)

(b) Tenofovir DF (TDF)

Important identified risks	<ul style="list-style-type: none"> · Renal toxicity · Post-treatment hepatic flares in HIV/HBV co-infected patients · Interaction with didanosine · Pancreatitis · Lactic acidosis and severe hepatomegaly with steatosis · Lipodystrophy
Important potential risks	Nil
Important missing information	<ul style="list-style-type: none"> · Safety in children · Safety in elderly patients · Safety in pregnancy · Safety in lactation · Safety in patients with renal impairment

(c) Emtricitabine (FTC)

Important identified risks	<ul style="list-style-type: none"> · Post-treatment hepatic flares in HIV/HBV co-infected patients · Lactic acidosis and severe hepatomegaly with steatosis · Lipodystrophy
Important potential risks	Nil
Important missing information	<ul style="list-style-type: none"> · Safety in elderly patients · Safety in pregnancy · Safety in lactation

(d) FTC/RPV/TDF FDC tablet

Important identified risks	Nil
Important potential risks	Overdose (occurring through accidental concurrent use of the FDC with any of its active components)
Important missing information	Safety information for the FDC product

Rilpivirine

RMP recommendations with respect to this section of the RMP have been included in the rilpivirine (RPV) single agent application, and the Delegate should consider these applicable to this combination product.⁶

Tenofovir DF*Additional safety concerns relating to patients co-infected with Hepatitis B virus (HBV)*

It is noted in a recent submission by the sponsor that the RMP includes several Ongoing Safety Concerns additional to those described in the RMP for this application. These are:

Important potential risk

- Development of drug resistance during long-term exposure in HBV infected patients.

Important missing information

- Safety in black HBV infected patients.
- Safety of long term exposure in HBV infected adults with compensated or decompensated liver disease.
- Safety in liver transplant recipients infected with HBV.

While the FDC product is not indicated for the treatment of chronic HBV infection in adults (as is single agent TDF), the sponsor should justify, in the context of the FDC treatment of HIV infected patients co infected with HBV, the exclusion of these safety concerns from the RMP for this application.⁷ Subject to the evaluation of the clinical safety specifications by the TGA's Office of Marketing Authorisation (OMA), the remaining Ongoing Safety Concerns for TDF, as specified by the sponsor, were considered acceptable

Emtricitabine*Safety in patients with renal impairment*

In the context of limited pharmacokinetic data relating to the safety of FTC in renal impairment and the exclusion of patients with moderate to severe renal impairment from the pivotal FTC trials it is recommended that, unless adequately justified, the sponsor include the safety in patients with renal impairment as important missing information in the RMP.⁸ Subject to the evaluation of the clinical safety specifications by the OMA, the remaining Ongoing Safety Concerns for FTC, as specified by the sponsor, were considered acceptable

⁶ The final agreed RMP for the fixed dose combination tenofovir/emtricitabine/rilpivirine product will be dependent on the outcome of the separate rilpivirine submission, including the RMP. For recommendations that directly address issues raised by the clinical evaluator for the rilpivirine submission, the Delegate is referred to the rilpivirine RMP evaluation report. These should all be considered as applicable to the combination product.

⁷ The Sponsor provided a response to the evaluator's request advising that the number of coinfecting HIV/HBV patients in Australia is low, and the use of Eviplera in co infected HIV/HBV patients is clearly described within the precautions section of the Eviplera PI.

⁸ The Sponsor provided a response to the evaluator's request advising the pivotal FTC trials included within the application to register Emtriva® were assessed by the TGA and further safety information associated with renal effects based on clinical and postmarketing experience and proper use of Emtriva in this setting of renal insufficiency are clearly presented in the Eviplera PI.

Pharmacovigilance Plan

Rilpivirine

For the all important potential risks the sponsor proposes routine pharmacovigilance (PhV)⁹ and the additional collection and evaluation of safety data from the ongoing and future planned clinical trials. The sponsor intends to present an analysis of the respective important potential risks in each periodic safety update report (PSUR).

With regard to the important missing information, RPV related pregnancy data from spontaneous reporting from the Antiretroviral Pregnancy Registry (APR) will monitored.

Background rate estimates provided by the sponsor for the important potential risks are summarised in Table 7. While the baseline incidence in HIV patients for these safety concerns is not well known, it is possible that the ongoing Phase III trials (TMC278-C209 and TMC278-C215) can detect increases in events above the background rate. These studies are less likely to inform the risk of serious skin reactions such as Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) which are rare events (rate in the general population is around 1 to 2 cases per million person years).

Table 7. Epidemiology of important potential risks in the background population unexposed to RPV. Table continued on the next page.

QT prolongation	<p><u>Prevalence</u></p> <p>The prevalence of QT interval prolongation in a cohort of asymptomatic HIV positive patients who were not taking any drug known to cause QT interval prolongation was estimated to be 28%.¹⁰</p>
Hepatotoxicity	<p><u>Incidence</u></p> <p>In a retrospective cohort study of 560 treatment-naïve patients receiving HAART therapy for the first time, 44 (7.9%) developed grade 4 liver enzyme elevations (LEE); and 95 (17%) developed grade 3+4 LEE. Symptoms occurred in less than 20% of the patients with grade 4 abnormalities</p>
Severe skin reactions	<p><u>Incidence</u></p> <p>Patients with AIDS have up to 1000-fold higher risk of developing SJS and TEN. Commonly caused by trimethoprim-sulfamethoxazole (TMP-SMX). TMP-SMX-related TEN in AIDS patients is 980 per 1 million. Nevirapine is the ARV most frequently associated with SJS/TEN¹¹</p>

⁹ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

¹⁰ Sani MU and Okeahialam BN. QTc interval prolongation in patients with HIV and AIDS. J. Nat. Med. Assoc. 2005; 12: 1657-1661

¹¹ Khambaty MM, Hsu SS. Dermatology of the patient with HIV. Emerg Med Clin North Am. 2010 May;28:355-68.

Table 7. continued.	
Depression	<p><u>Prevalence</u></p> <p>Estimates of the prevalence of depression among HIV infected patients range from 0% to 47.8%. It has been estimated that HIV-infected individuals are twice as likely to be diagnosed with major depression compared to sero-negative patients.¹²</p>

Finally, the FDA postmarketing requirement of a drug interaction study (steady state RPV and single dose digoxin pharmacokinetics) should be included in the Australian RMP with milestones for reporting identified.

Additional PhV recommendations based on the clinical evaluation for the single agent RPV submission have not been included in this RMP evaluation report and the Delegate should refer to the single agent report.

Tenofovir DF

In addition to routine PhV, the following additional PhV actions are planned:

Important identified risk: Renal toxicity

- *Observational cohort study in adults with HIV (EuroSIDA Cohort Study).* The sponsor states that this study will provide information on the incidence of renal toxicity with TDF. The study was ongoing at the time of this evaluation.
- *Clinical studies in HIV infected patients (GS-99-903 and ACTG 5202)* are proposed to provide information on bone toxicity with long-term exposure to TDF.
- *Observational case control study (GS-US-104-0353).*
- *Nonclinical studies on intestinal phosphate absorption.*

Important missing information: Safety in pregnancy

- *APR*, as described above with respect to RPV, will provide information on the risk of birth defects in patients exposed to TDF during pregnancy.
- *Cross sectional study 'MITOC'.* This study is ongoing.

Important missing information: Safety in patients with renal impairment

- Study GS-US-174-0121.
- Study GS-US-174-0127.
- GS-US-174-0108. The study has commenced.
- GS-US-203-0107. The study has commenced.

¹² Chander G, Himelhoch S, Moore RD. Substance abuse and psychiatric disorders in HIV-positive patients: epidemiology and impact on antiretroviral therapy. *Drugs*. 2006;66:769-89.

OPR evaluator comments

Additional safety concerns relating to patients co infected with Hepatitis B virus (HBV) were noted from a recent submission by the sponsor. Unless exclusion of these Ongoing Safety Concerns from the FDC RMP can be justified, an adequate PhV plan for these should be proposed by the sponsor.

Concerning the *Important identified risk of renal toxicity*:

- The incidence of acute renal failure in HIV infected patients has been estimated to range from 2.7 – 5.9 per 100 person years.^{13,14} Given this relatively high background rate, it is likely that studies proposed to provide additional PhV for the identified risk of renal toxicity will be able to detect an increase frequency from background.
- The milestones for reporting of the EuroSIDA cohort study safety data analyses are not clearly identified (it is stated that the sponsor receives regular updates from the collaboration). The sponsor should clarify the frequency of analysis reporting and how these will be made known to the TGA. The sponsor should provide a synopsis of the nonclinical studies on intestinal phosphate absorption. Although such studies are outlined as planned, the milestone for data availability is February 2011 and therefore, if completed, any significant findings that have potential relevance to human safety should be provided.

Concerning *Important missing information on the safety of TDF in patients with renal impairment*:

- While studies *GS-US-174-0108* and *GS-US-203-0107* do not exclude patients with mild and mild to moderate renal impairment respectively, they may not necessarily provide additional information on the safety in patients with renal impairment as the inclusion of such patients is not a study requirement and therefore it is unknown how many renally impaired patients have been enrolled. *Study GS-US-174-0121* will more specifically provide pharmacokinetic and safety information from patients with renal impairment treated with TDF.

The remaining PhV actions for TDF were considered acceptable at this time.

Emtricitabine

In addition to routine PhV, additional actions are planned to provide information on the safety of FTC in pregnancy. These are the ARV Pregnancy Registry and the MITOC study as described above.

Unless the exclusion of missing information on the safety of FTC in renally impaired patients as an Ongoing Safety Concern can be adequately justified, an appropriate PhV plan should be proposed by the sponsor for this area of important missing information.

The remaining PhV actions for FTC were considered acceptable at this time.

FDC product

Subject to the evaluation of the clinical safety specifications by the OMA, the Ongoing Safety Concerns for the FDC product, as specified by the sponsor, were considered acceptable.

¹³ Franceschini N, Napravnik S, Eron JJ, Jr., Szczech LA, Finn WF. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. *Kidney Int* 2005;67:1526-31.

¹⁴ Roe J, Campbell LJ, Ibrahim F, Hendry BM, Post FA. HIV care and the incidence of acute renal failure. *Clin Infect Dis* 2008;47:242-9.

Further characterisation of the safety profile of the FDC product is proposed from the analysis of safety data (adverse events and clinical laboratory tests) from planned studies.

Except for the renal toxicity safety concern associated with the TDF component of the FDC, the sponsor has concluded that routine risk minimisation¹⁵, by way of product labelling, was sufficient to manage the Ongoing Safety Concerns.

The APR is an international pregnancy registry and therefore Australian patients are presumably eligible for inclusion. It was recommended that the sponsor provide information about how health care professionals (HCP) will be made aware of the existence of the Registry and the procedures for registering a patient. For example, in the US the product label for RPV provides a synopsis of the Registry particulars and contact details in the pregnancy section.¹⁶ The open label Phase III study (GS-US-264-0106) is considered adequate to provide further information on the short and long-term safety profile of the FDC product.

Risk Minimisation Activities

The additional risk minimisation activity recommended by the sponsor relates to mitigating the risk of renal toxicity with the TDF component. It is planned to achieve this through a HIV educational program for healthcare providers. The sponsor stated that this program is primarily aimed at communicating the importance of assessing CrCl at baseline and during therapy and the need for appropriate dose reduction in patients with renal impairment. The sponsor has plans to update the program to include the FDC. The sponsor asserted that promotional materials supplied were in line with the Medicines Australia Code of Conduct. It was proposed to review this risk minimisation activity by further 'waves of research' that 'will assess changes in knowledge/awareness over time following the implementation of educational campaigns as appropriate'.

OPR evaluator comment

While the healthcare provider educational program in principle was considered acceptable, it was recommended that the sponsor please provide further clarifying information regarding this risk minimisation activity to include, but not necessarily be restricted to, the following:

- A summary description of the planned educational program for implementation following approval of the FDC product.
- Will new educational material be provided to prescribers including emphasis on specific differences between Viread (TDF) and the FDC product with respect to mitigating renal risk (for example, FDC product should not be used in patients with mild to moderate renal impairment as dose interval reduction cannot be achieved with the FDC)?
- Details on the research proposed to assess changes in prescriber knowledge/awareness over time and how these will specifically assess the effectiveness, or not, of the risk minimisation activity?
- How will the results of research to assess the effectiveness of the educational program be made known to the TGA?

¹⁵ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

¹⁶ The Sponsor provided a response to the evaluators request advising that HCP's would be made aware of the APR during commercial launch activities and appropriate internal procedures would assure follow up of pregnancy outcomes.

Routine risk minimisation was considered adequate at this stage for the remaining Ongoing Safety Concerns given that prescribing would be by specialists or those with experience in the area of HIV medicine.¹⁷

Summary of Recommendations

The following is a summary of the recommendations to the Delegate. For recommendations that directly address issues raised by the clinical evaluator for the rilpivirine submission, the Delegate is referred to the rilpivirine RMP evaluation report. These should all be considered as applicable to the combination product. It was suggested that the sponsor update the Australian RMP with respect to the recommended amendments and additional activities. If the sponsor does not agree with any of the particular recommendations, adequate justification as to why that recommendation should not be implemented should be provided. It was recommended that if significant additional safety concerns are identified by the clinical evaluator, they should be addressed in the RMP by the sponsor.

Safety specifications. Clinical

In the context of limited pharmacokinetic data relating to the use of FTC in renal impairment and the exclusion of patients with moderate to severe renal impairment from the pivotal FTC trials (FTC-301A, FTC-302, FTC-303 and ANRS 099), the statement that 'there is currently no evidence of significant toxicity (particularly renal toxicity) of FTC which might be associated with higher drug exposure in renally impaired patients' requires justification by the sponsor so that the appropriateness of excluding this area of missing information as an ongoing safety concern can be evaluated. It was recommended that the sponsor clearly distinguish between evidence from clinical trials that have included and monitored patients with moderate to severe renal impairment and evidence inferred from postmarket spontaneous adverse event reporting in their justification.

Ongoing Safety Concerns

It is noted in a recent submission by the sponsor the RMP includes several Ongoing Safety Concerns additional to those described in the RMP for this application (see above for details). While the FDC product is not indicated for the treatment of chronic HBV infection in adults as is single agent TDF, the sponsor should justify, in the context of the FDC treatment of HIV infected patients co-infected with HBV, the exclusion of these safety concerns from the RMP for this application.

Pharmacovigilance plan

- Provide a milestone for reporting results from the FDA postmarket requirement for a drug interaction study (single dose digoxin pharmacokinetics).
- The APR is an international pregnancy registry and therefore Australian patients are presumably eligible for inclusion. It is recommended that the sponsor provide information about how health care professionals (HCP) will be made aware of the existence of the registry and the procedures for reporting. For example, in the US the product label for RPV provides a synopsis of the Registry in the pregnancy section.
- For the additional *Ongoing Safety Concerns* identified in the TDF RMP of another recent submission by the sponsor as outlined above, it is recommended that the sponsor provide an adequate PhV action plan for these safety concerns unless adequate justification is provided for not including these in the RMP.

¹⁷ The sponsor provided information to the TGA in relation to the above listed requests.

- With respect to the EuroSIDA cohort study the sponsor should clarify the frequency of analysis reporting and how these will be made known to the TGA.
- Protocols for studies listed in the PhV plan should be provided for review if the study has not yet commenced. It is also recommended that milestones for reporting interim/final results to the TGA are provided.

Risk minimisation plan

While the healthcare provider educational program in principle is acceptable, it was recommended that the sponsor please provide further clarifying information regarding this risk minimisation activity to include, but not necessarily be restricted to, the points outlined above (*Risk Minimisation Activities; OPR evaluator comment*).

Updates to the proposed PI and Consumer Medicines Information were also recommended.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The drug substances tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) are highly soluble in aqueous media while rilpivirine (RPV) is practically insoluble across the physiological pH range. The routine quality control dissolution method applied to the fixed tablets was based on that proposed for rilpivirine tablets.

The drug product has been formulated using commonly used excipients that comply with the standards defined in current USP/NF and Ph. Eur. monographs.

The single dose bioequivalent study (Study GS-US-264-0103) in support of the current Australian submission was a three way crossover trial in which 2 fixed dose formulations (F3 and F4) containing TDF 300mg/FTC 200mg/RPV 25mg were compared with the three single agent reference products (TDF 300mg; FTC 200mg; RPV 25mg) which were administered concomitantly. As food is known to increase the bioavailability of TDF and RPV, the study was conducted under fed conditions.

Based on bioequivalent limit of 80-125%, both fixed dose test formulations (F3 and F4) were bioequivalent to the concomitant administration of three single agent products with regard to AUC and C_{max} for TDF and FTC.

Relatively higher mean AUC and C_{max} with regard to rilpivirine were obtained with both fixed dose test formulations compared to administration of the 3 single agents concomitantly. The F4 formulation failed on account of upper limit of 90% CI for rilpivirine C_{max} . The rilpivirine results (AUC and C_{max}) results were with 80-125% for the F3 formulation but it was also supra bioavailable (whole 90% CI above 100% with point estimates around 115%). Note that F3 also showed significantly higher C_{max} for TDF and FTC with point estimates around 111% and 105%, respectively.

The sponsor had earlier investigated two other fixed dose formulations (F1 and F2) which gave 50% greater C_{max} and 35% greater AUC for rilpivirine.

The quality evaluator has commented that the significantly higher bioavailability of rilpivirine in these formulations suggests that the rilpivirine single agent tablet is not optimally formulated and this has necessitated the development of a triple combination tablet that is also sub optimally formulated with respect to rilpivirine. This is of some

concern because a sub optimally formulated product may display inconsistent bioavailability from batch to batch. ²

Otherwise there was no objection to registration of Eviplera tablets from the quality evaluator. The current Australian submission was to be reviewed at the November 2011 meeting of the Pharmaceutical Subcommittee (PSC) whose advice should thus be available to the ACPM at its December 2011 meeting.

The following Pharmaceutical Subcommittee Recommendation No 2240, as ratified on 28 November 2011 and accepted by ACPM on 1 December 2011, was noted:

1. The PSC endorsed all the questions raised by the TGA in relation to pharmaceutical and biopharmaceutical aspects of the submission by Gilead Sciences Pty Ltd to register Eviplera film coated tablet containing 300 mg / 200 mg / 25 mg of tenofovir disoproxil fumarate / emtricitabine / rilpivirine (as hydrochloride). In particular, the Committee supported the evaluator's request that the sponsor should specify that rilpivirine is present in the drug product as the hydrochloride salt.
2. The Committee advised that all outstanding issues should be addressed to the satisfaction of the TGA.
3. The PSC supported the evaluator's conclusion that both the single agent and triple agent rilpivirine products were sub optimally formulated. This is of some concern as a sub-optimally formulated product may display inconsistent/variable bioavailability from batch to batch. The Committee therefore agreed that the impact of variable bioavailability on efficacy required clinical interpretation to place this issue in context.
4. The Committee noted that the dissolution profiles of rilpivirine from various tablet formulations supported the sponsor's claim that the dissolution of rilpivirine is enhanced by the presence of the other two drug substances in the formulation.
5. The PSC considered that the sponsor should be asked to:
 - Provide batch analysis data on three consecutive validation batches.
 - Ensure that drug substances from all the nominated manufacturing sites are included in future revalidation and stability trials.

Nonclinical

The sponsor submitted 3 *in vitro* studies in acutely infected MT-2 cells which demonstrated synergistic anti HIV-1 activity with the proposed combination. Resistance selection experiments yielded breakthrough mutations M184I after 22 days at 1.7 times the EC₅₀ for TDF + FTC + RPV and K65R after 49 days at 3.3 times the EC₅₀. No further RT mutations were detected with higher multiples of EC₅₀ values. Results of a cross resistance study indicate that HIV-1 strains with rilpivirine associated mutations show lack of cross resistance to emtricitabine and tenofovir.

Adequate justification was provided for the lack of nonclinical toxicity studies with the fixed triple combination, which was consistent with the TGA adopted EU guideline⁴ and was based on the nonclinical safety profiles for each of these compounds, the substantial clinical experience with emtricitabine and tenofovir in antiretroviral combination therapy for the treatment of HIV-1 infection and on Phase II and Phase III clinical experience with rilpivirine.

The sponsor has provided updated specifications providing limits for the two newly identified emtricitabine impurities. These impurities were present in a degraded preparation of emtricitabine and tenofovir, which was administered to rats as part of a 14 day repeat dose toxicity study previously evaluated by the TGA. Based on the NOAEL for the impurities in this study, the exposure to these impurities (weight/body surface area) was approximately 9 times the anticipated human exposure. It was therefore considered that the two impurities have been adequately qualified.

The two impurities have not been qualified in genotoxicity studies, as recommended by the EU guidelines for impurities in new drug products at levels above the qualification threshold⁵. An *in silico* screen was negative but this is not considered to be an acceptable surrogate for *in vitro* screening. However, the nonclinical evaluator considered the lack of genotoxicity data with the two degradants to be acceptable based on a similarity in structure with the parent compound and due to the need for adequate therapies for a life threatening condition.

The sponsor has provided adequate justification for the lack of nonclinical toxicity studies with the triple combination. The two recently identified emtricitabine degradants were adequately tested in a 2 week toxicity study with negative results. A minimum genotoxicity screen has not been conducted with either degradant. The nonclinical evaluator has accepted the potential on the basis of clinical need for treatment of a life threatening condition.

Clinical

This application has been cross referenced to the clinical data submitted for the registration of rilpivirine 25mg oral tablets which will also be considered at the same ACPM meeting.

The relevant clinical studies include two pivotal Phase III trials (C209 and C115). The former compared TDF/FTC/RPV to TDF/FTC/EFV whereas in the latter RPV was compared to EFV against background of investigator selected ARTs including TDF/FTC. In this latter trial, TDF/FTC background therapy was used by 59.9% trial participants. Both studies were randomised, double (dummy) blinded in adult HIV-1 patients (baseline viral load ≥ 5000 copies/mL) who were ART treatment naïve at baseline. The non inferiority (no worse than -10%) with respect to proportion of patients with primary efficacy outcome of viral load < 50 copies/mL at 48 weeks was satisfactorily demonstrated in both trials although overall higher virologic failure was seen in rilpivirine treated patients (9.0%) compared to the efavirenz treated (4.8%) patients. Rilpivirine showed dose related toxicity with incidences of rash and prolonged QT interval¹⁸. However, at the proposed clinical dose of 25 mg daily the risk appears to be low. Rilpivirine also interferes with adrenal steroid hormone synthesis although its clinical significance at 48 weeks was not clear.

The drug-drug interaction studies included in the rilpivirine included NRTIs TDF and didanosine. The rilpivirine PK parameters were comparable when given alone or when co administered with TDF whereas the mean tenofovir C_{max} and AUC_{24h} were about 1.2 fold higher on co administration with rilpivirine compared to administration alone. No clinical relevant changes were observed in PK of either drug during co administration with didanosine compared to administration of rilpivirine alone. This proposed fixed agent includes NRTI emtricitabine in addition to TDF (and RPV). Based on results obtained in these drug interaction studies and existing clinical information, no dose adjustment of

¹⁸ QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

rilpivirine is proposed with NRTIs including emtricitabine. This was considered satisfactory.

Risk Management Plan

The RMP evaluator has commented that safety of FTC in impaired renal function was important missing information in the RMP. The sponsor was requested to provide further comments with respect to this.

A recommendation was also made that a cautionary statement be included in the drug interactions section regarding the potential for drugs that decrease renal function or compete for active tubular secretion to increase serum concentrations of TDF, FTC or coadministered drugs as in the Truvada product information. The sponsor was requested to provide comments in their pre ACPM response.

The RMP itself was considered acceptable and the following specific condition of registration was recommended:

The full implementation of the Risk Management Plan for Australia, Version 0.1, dated 18 August 2010.

Risk-Benefit Analysis

Delegate Considerations

Tenofovir DF (Viread), Emtricitabine (Emtriva), the fixed dose double combination TDF/FTC (300/200mg Truvada) and a fixed dose triple combination TDF/FTC/EFV (300/200/600mg Atripla) are currently registered in Australia for treatment of HIV infection in various population groups with respect to age and past history of antiretroviral treatment.

The proposed doses of two (TDF 300mg/FTC 200mg daily) of the three individual components of the fixed dose triple agent combination are the same as those recommended for the individual drugs. The third agent (RPV) was evaluated concurrently as a single agent product and it was also before the ACPM for advice. Its proposed dose (25mg daily) in the fixed combination is also same as that in the proposed single agent product. All three are dosed once daily and can (should) be taken with meals.

The rationale for the fixed dose combination includes patient convenience for a new NNRTI (rilpivirine) with currently accepted backbone ART. The ADME¹⁹ features of the three drugs support combined administration.

Adequate clinical data supporting the clinical efficacy and documenting the adverse effects profile of TDF/FTC/RPV were included in the rilpivirine application and were applicable to this fixed dose combination.

This submission primarily relies on a bioequivalence study. The forthcoming advice from the PSC is expected to cover the issue of a poorer formulation and risk of batch to batch variability necessitated by supra available rilpivirine in the fixed dose combination.

In addition, the ACPM was asked to provide guidance on the clinical significance of 10-15% higher bioavailability of drugs in the fixed dose combination.

This application is clearly contingent on advice from the PSC and the ACPM with respect this fixed dose combination and the ACPM advice in regard to the rilpivirine single agent.

Pending this advice, the Delegate considered that the TDF 300mg/FTC 200mg/RPV 25mg fixed dose combination tablet may be suitable for approval in a population consistent with

¹⁹ Pharmacokinetics: Absorption, Distribution, Metabolism and Excretion (ADME)

the most restrictive therapeutic indication applicable to its components in the treatment of HIV-1 infection.

Delegate's Proposed Action

Pending advice from the PSC and the ACPM, the Delegate proposed the following therapeutic indication for Eviplera (TDF/FTC/RPV 300/200/25mg) fixed dose combination tablet:

Eviplera is indicated for the treatment of HIV-1 infection in treatment-naïve adult patients.

One tablet one daily taken orally with a meal.

Eviplera is not recommended for use in patients with moderate or severe renal impairment (Creatinine Clearance < 50mL/min). Patients with moderate or severe renal failure require dose intervals of tenofovir DF and emtricitabine that cannot be achieved with the combination tablets (see Precautions).

It is also recommended that the *Dosage and Administration* section in the PI should include a statement that Eviplera should not be given to patients with severe hepatic impairment.

Advice from the ACPM was requested.

Response from Sponsor

Gilead supported the proposed actions of the Delegate. However the sponsor did not agree with the proposed wording of the indication for Eviplera tablets. For the reasons presented below, the sponsor proposed that Eviplera should be approved for the following indication:

Eviplera is indicated for the treatment of HIV infection in treatment-naïve adult patients or who have no known resistance to the individual components of Eviplera.

Sponsor's Summary

Gilead has co-formulated rilpivirine (RPV), a potent non nucleoside reverse transcriptase inhibitor (NNRTI), with the standard-of-care NRTI backbone tenofovir DF/emtricitabine (TDF/FTC) into a fixed dose combination (FDC) tablet. This FDC represents a significant benefit to HIV infected patients due to simplified dosing. Eviplera tablets have the potential to combine a next generation NNRTI, with the standard-of-care, preferred-agent NRTIs TDF and FTC. Eviplera would potentially be the second highly active, once daily FDC regimen, and will address limitations with the only other fixed dose regimen (ATRIPLA®). Eviplera offers an attractive treatment option to a significant number of patients. Therefore, there remains a need for new combinations of potent agents exhibiting favourable tolerability, minimal short and long term toxicity and convenient dosing to maximise patient adherence.

Most antiretroviral treatment guidelines¹ recommend testing the susceptibility profile of a patient's HIV in order to guide the selection of a combination antiretroviral therapy. The sponsor therefore believed that the use of Eviplera tablets should be guided by resistance testing and not be limited for use only in treatment-naïve patients with HIV-1 infection. An indication for use in treatment naïve patients alone will provide an unwarranted barrier to use of this new therapeutic option for patients with no known resistance to the components of Eviplera, who can be expected to respond favourably to the use of Eviplera in the treatment of their HIV-1 infection.

Gilead noted the Delegate's concerns regarding bioavailability of the proposed formulation and the potential for batch to batch variability of the FDC tablet. These concerns were raised with Gilead during evaluation and the TGA evaluator noted in their responses that

“on a risk management basis, no further action would be required.”

The formulation of Eviplera selected for commercialisation achieved bioequivalence as assessed by C_{max} , AUC_{last} , and AUC_{inf} . The attributes of the formulation that contributed to the bioequivalence with the single agent tablets have been identified and are well controlled during manufacture with appropriate in process testing and control of critical steps. Testing of the process has been routinely performed during manufacture to demonstrate consistency from batch to batch. Assurance was provided that any batch identified to be below the approved release specifications will not be released to the Australian market. Therefore, based on the sponsor's thorough understanding of the formulation characteristics, strict manufacturing and release testing, the sponsor strongly believed that there would be no formulation attributable variability in bioavailability between batches. In addition, identical formulations of Eviplera are registered in the US and Canada (Complera™), and proposed for registration in Europe. The remainder of this response is separated into three sections.

Indication Statement

The Delegate's overview states that the Eviplera FDC tablet may be suitable for approval in a population consistent with the most restrictive therapeutic indication applicable to its components in the treatment of HIV infection. The sponsor did not agree with the changes proposed to the indication.

TDF and FTC are antiretroviral agents developed by the sponsor that have been approved for the treatment of HIV infection as the stand alone agents Emtriva® and Viread®, and in a FDC product Truvada® (TDF/FTC). FTC and TDF are also approved for the treatment of HIV-1 infection in a FDC product with EFV, a NNRTI, known as Atripla.

The sponsor has co formulated RPV, a potent NNRTI, with the standard-of-care NRTI backbone TDF/FTC into a FDC tablet to be administered once daily with a meal. The FDC of Eviplera has the potential to combine a next generation NNRTI, with the standard of care, preferred agent NRTIs TDF and FTC. This fixed dose regimen would potentially be the second highly active, once daily FDC regimen, and will address limitations with the only other fixed dose regimen (Atripla). Eviplera offers an attractive treatment option to a significant number of patients. The proposed indication therefore excludes patients who cannot tolerate the side effects and require an alternative therapy.

The current Australian application is supported by data from Study GS-US-264-0103 (0103), which establishes bioequivalence between the FDC tablet and the concurrent administration of the individual agents and by cross reference to the clinical efficacy and safety data previously evaluated and accepted by the TGA for the products Viread, Emtriva, Truvada and Atripla, in treatment naïve and treatment experienced adults.

The application was also supported by cross reference to the RPV single agent application filed by Janssen Australia. Two Phase III studies (C209 and C215) support the use of RPV in combination with other HIV agents in treatment-naïve patients. It is further supported by the 96 week efficacy and safety analysis of the dose finding Phase IIb study (C204) and long term data up to 192 weeks of that same trial also support the Eviplera application. In addition, a study with RPV was conducted in approximately 40 treatment experienced HIV-1 infected patients (StudyR27874-C202).

Most antiretroviral treatment guidelines²⁰ recommend testing the susceptibility profile of a patient's HIV in order to guide the selection of a combination antiretroviral therapy. Gilead therefore believes that the use of Eviplera tablets should be guided by resistance testing and not be limited for use only in treatment naïve patients with HIV-1 infection. A limited indication for use in treatment naïve patients will provide an unnecessary barrier for use of this new therapeutic option for patients with no known resistance to the components of Eviplera, who can be expected to respond favourably to the use of Eviplera in the treatment of their HIV-1 infection. Gilead therefore proposes an alternative indication for Eviplera as follows:

Eviplera is indicated for the treatment of HIV infection in treatment-naïve adult patients or who have no known resistance to the individual components of Eviplera.

Formulation

One of the main objectives during formulation optimisation of the FDC tablets was to demonstrate bioequivalence of all three active ingredients with respect to the commercial formulations of Emtriva and Viread, and the Phase III/commercial RPV tablet administered concurrently.

During development, four tablet formulations were investigated and human bioequivalence studies were used to guide the selection of the appropriate formulation and manufacturing process. Study GS-US-264-0101 (0101) evaluated Formulations 1 (F1) and 2 (F2) and Study GS-US-264-0103 (0103) evaluated Formulations 3 (F3) and 4 (F4) for bioavailability/bioequivalence relative to co administration of the individual components.

F1 and F2 both failed to demonstrate bioequivalence for RPV in Study 0101 with significantly higher AUC and C_{max} than those obtained with the RPV Phase III clinical formulation. In contrast, both FTC and TDF AUC and C_{max} levels for F1 and F2 were bioequivalent to the commercial formulations of Emtriva and Viread, respectively. In Study 0103, F4 failed to achieve bioequivalence with respect to RPV exposure. F3 achieved bioequivalence as assessed by C_{max} , the area under the plasma concentration time curve from time zero to the last measurable time point (AUC_{last}) and area under the plasma concentration time curve from time zero to infinity (AUC_{inf}) for all analytes and was selected as the commercial formulation. Differences in the design and composition of F3 and F4 accounts for the difference in bioavailability observed.

During TGA evaluation of the application, Gilead provided *in vitro* dissolution profiles comparing primary stability lots and three process validation batches demonstrating that the release of RPV from the F3 tablet is consistent from batch to batch. In addition, comparison of the dissolution profiles for RPV in three process validation lots with primary stability lots was able to correctly reflect the difference in the bioavailability of RPV in F1 and F2 and formulations F3 and F4 and the RPV single-agent tablet. The consistent dissolution of the three process validation lots and primary stability lots strongly supports the evidence that the bioavailability of rilpivirine from routine commercial lot manufacture will be consistent.

Following review of this data, the TGA evaluator commented that

“on a risk management basis, no further action would be required”.

The attributes of the formulation that contributed to the bioequivalence with the single agent tablets have been identified and are well controlled during manufacture with

²⁰ Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services, January 10, 2011; 1-166

appropriate in process testing and control of critical steps. Testing of the process has been routinely performed during manufacture to demonstrate consistency from batch to batch. Assurance is provided that any batch identified to not meet the proposed release specifications will not be released to the Australian market.

Therefore, based on Gilead's thorough understanding of the formulation characteristics, strict manufacturing controls and release testing, Gilead strongly believes that there would be no variability attributable to the formulation in the bioavailability of the drug components between batches.

In addition, the same identical formulation of Eviplera is approved and registered in the US and Canada (under the trade name Complera), and has received Committee for Medicinal Products for Human Use (CHMP) Positive Opinion in Europe.

Risk Management Plan (RMP)

The RMP evaluator has considered the proposed RMP to be acceptable and has recommended:

“full implementation of the RMP for Australia, Version 0.1 dated 18 August 2010.”

Advisory Committee Considerations

The current application was for a new combination of currently registered active ingredients and was therefore cross referenced to the ingredient, rilpivirine.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy

The ACPM agreed with the Delegate that the submission provided sufficient evidence of efficacy to support the application for a defined population group. The predefined subgroup with >100,000 cp/mL HIV RNA at baseline had a higher incidence of virological failure and consequent resistance to this product, as well as for background nucleoside reverse transcriptase inhibitors and therefore cross resistance within the class. Therefore, in this population this product does not meet benefit-risk threshold.

Safety

The ACPM agreed with the Delegate that the safety profile of this product was sufficiently defined to support the application. In addition, the committee noted that the single trial investigating hepatic impairment included only small numbers and was inadequate to determine risk and the small increase in serum creatinine in neuro-psych adverse events and unexpected cortisol reduction should be considered for periodic monitoring.

Indication

The ACPM considered this product to have a positive benefit-risk profile for the indication of:

Eviplera: treatment of HIV-1 infection in treatment-naive adult patients with plasma HIV RNA < 100,000 copies per mL at start of therapy. One tablet once daily taken orally with a meal.

Eviplera is not recommended for use in patients with moderate or severe renal impairment (Creatinine Clearance <50 mL/min). Patients with moderate or severe renal failure require dose intervals of tenofovir DF and emtricitabine that cannot be achieved with the combination tablets (see Precautions).

PI/ CMI:

The ACPM recommended additional changes to the Product Information (PI) and Consumer Medicines Information (CMI) but these are beyond the scope of the AusPAR.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Eviplera film coated tablet would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Eviplera tablets containing Tenofovir disoproxil fumarate 300 mg, Emtricitabine 200 mg and Rilpivirine (as HCl) 25 mg for oral administration, indicated for:

The treatment of HIV infection in treatment-naïve adult patients with plasma HIV-1 RNA \leq 100,000 copies/mL at the start of therapy.

The following Specific Condition Apply to this Therapeutic Good:

1. Full implementation of the Risk Management Plan in Australia version 0.1, dated 18 August 2010 for Eviplera (fixed dose combination of 300 mg of tenofovir disoproxil fumarate, 200 mg of emtricitabine and 25 mg of rilpivirine), and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

www.tga.gov.au

Reference/Publication #

Product Information

EVIPLERA[®] (tenofovir disoproxil fumarate, emtricitabine and rilpivirine) tablets

NAME OF THE MEDICINE

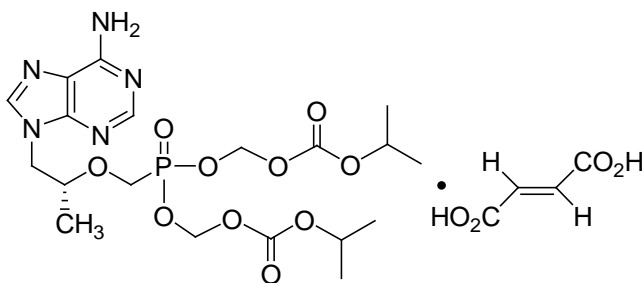
EVIPLERA (300 mg tenofovir disoproxil fumarate/200 mg emtricitabine/25 mg rilpivirine) tablets.

The active substances in EVIPLERA tablets are tenofovir disoproxil fumarate (tenofovir DF), emtricitabine and rilpivirine hydrochloride.

VIREAD[®] is the brand name for tenofovir DF, which is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. EMTRIVA[®] is the brand name for emtricitabine (FTC), a synthetic nucleoside analog of cytidine. EDURANT[®] is the brand name for rilpivirine, a non-nucleoside reverse transcriptase inhibitor. All three compounds exhibit activity against HIV-1 reverse transcriptase. Tenofovir DF and emtricitabine are the components of TRUVADA[®].

DESCRIPTION

Tenofovir disoproxil fumarate: Tenofovir DF is a fumaric acid salt of the *bis*-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir DF is 9-[(*R*)-2 [[bis[[isopropoxycarbonyl]oxy] methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of C₁₉H₃₀N₅O₁₀P • C₄H₄O₄ and a molecular weight of 635.52. It has the following structural formula:

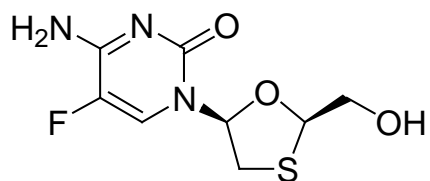


CAS registry number: 202138-50-9

Tenofovir DF is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (*log p*) for tenofovir disoproxil is 1.25 and the pKa is 3.75.

Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of C₈H₁₀FN₃O₃S and a molecular weight of 247.24. It has the following structural formula:



CAS registry number: 143491-57-0

Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 °C. The partition coefficient ($\log p$) for emtricitabine is -0.43 and the pKa is 2.65.

Rilpivirine: Rilpivirine is present in EVIPLERA tablets as the hydrochloride salt. The chemical name for rilpivirine hydrochloride is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl] amino]benzotrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6 \bullet HCl$ and its molecular weight is 402.88. Rilpivirine hydrochloride has the following structural formula:

CAS registry number: 700361-47-3

Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water and over a wide pH range.

EVIPLERA tablets contain the following ingredients as excipients:

Tablet core: Pregelatinized starch, lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, polysorbate 20. *Film-coating:* Macrogol 3350, hypromellose, lactose, glycerol triacetate, titanium dioxide, iron oxide red, indigo carmine aluminium lake, sunset yellow FCF aluminium lake

Each EVIPLERA tablet is capsule shaped, film-coated and purplish-pink in colour. Each tablet is debossed with 'GSI' on one side and plain on the other side. The tablets are supplied in bottles with child resistant closures.

PHARMACOLOGY

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC code: J05AR06.

Mechanism of action

Tenofovir disoproxil fumarate: is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir DF requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of human immunodeficiency virus-type 1 (HIV-1) reverse transcriptase (RT) by competing with the natural substrate deoxyadenosine 5'-triphosphate

and, after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

Emtricitabine: a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α , β , ϵ and mitochondrial DNA polymerase γ .

Rilpivirine: Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 RT. Rilpivirine does not inhibit the human cellular DNA polymerase α , β , and mitochondrial DNA polymerase γ .

Antiviral activity *in vitro*

Tenofovir disoproxil fumarate, emtricitabine and rilpivirine: The triple combination of tenofovir, emtricitabine and rilpivirine demonstrated synergistic antiviral activity in cell culture.

Tenofovir disoproxil fumarate: The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50% inhibitory concentration) values for tenofovir were in the range of 0.04 to 8.5 μ M. In drug combination studies of tenofovir with nucleoside analogue reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine (3TC), stavudine (d4T), zalcitabine, zidovudine (AZT)), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O (IC_{50} values ranged from 0.5 to 2.2 μ M). In addition, tenofovir has also been shown to be active *in vitro* against HIV-2, with similar potency as observed against HIV-1.

Emtricitabine: The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The IC_{50} value for emtricitabine was in the range of 0.0013 to 0.64 μ M (0.0003 to 0.158 μ g/mL). In drug combination studies of emtricitabine with NRTIs (abacavir, 3TC, d4T, zalcitabine, AZT), NNRTIs (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 μ M) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 μ M).

Rilpivirine: Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM. Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2510 to 10830 nM, treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data. Rilpivirine demonstrated antiviral activity against a broad panel of HIV-

1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC₅₀ values ranging from 0.07 to 1.01 nM and group O primary isolates with EC₅₀ values ranging from 2.88 to 8.45 nM. Rilpivirine showed additive to synergistic antiviral activity in combination with the N(t)RTIs abacavir, didanosine, emtricitabine, 3TC, d4T, tenofovir, and AZT; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide; the entry inhibitor maraviroc; and the integrase inhibitor raltegravir.

Drug Resistance

In Cell Culture:

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected *in vitro*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Rilpivirine: Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The most commonly observed amino acid substitutions that emerged included: L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

In Clinical Studies:

Tenofovir disoproxil fumarate, emtricitabine, and rilpivirine: In a pooled analysis for patients receiving rilpivirine in combination with tenofovir DF/emtricitabine in clinical trials C209 and C215 [see CLINICAL TRIALS], there were 62 virologic failure patients with resistance information available for 54 of those patients. The amino acid substitutions associated with NNRTI resistance that developed most commonly in these patients were: V90I, K101E, E138K/Q, Y181C, V189I, and H221Y. However, the presence of the substitutions V90I and V189I at baseline did not affect the viral response. The amino acid substitutions associated with NRTI resistance that developed in 3 or more patients were: K65R, K70E, M184V/I, and K219E during the treatment period.

Cross-resistance:

Tenofovir disoproxil fumarate, emtricitabine and rilpivirine:

No significant cross-resistance has been demonstrated between rilpivirine-resistant HIV-1 variants and emtricitabine or tenofovir, or between emtricitabine- or tenofovir-resistant variants and rilpivirine.

In Clinical Studies:

In a pooled analysis for patients receiving rilpivirine in combination with tenofovir DF/emtricitabine in clinical trials C209 and C215 [see CLINICAL TRIALS], 54 patients with virologic failure had available phenotypic resistance data at virologic failure, 37 lost susceptibility to emtricitabine, 29 lost susceptibility to rilpivirine, and 2 lost susceptibility to tenofovir DF. Among these subjects, 37 were resistant to 3TC, 28 were resistant to etravirine, 26 to efavirenz, and 12 to nevirapine. Reduced susceptibility was observed to abacavir and/or didanosine in some cases.

Tenofovir disoproxil fumarate: The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and 3TC. Therefore, cross-resistance among these drugs may occur in patients whose virus harbours the K65R mutation. Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir DF. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir. HIV-1 containing the substitutions associated with NNRTI resistance K103N and Y181C, or rilpivirine-associated substitutions were susceptible to tenofovir.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to 3TC and zalcitabine but retained sensitivity to abacavir, didanosine, d4T, tenofovir, AZT, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to d4T and AZT (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the substitutions associated with NNRTI resistance K103N or rilpivirine-associated substitutions were susceptible to emtricitabine.

Rilpivirine: In a panel of 67 HIV-1 recombinant laboratory strains with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V.

In the pooled analysis of all patients in the clinical trials C209 and C215, 31 of the 62 patients with virologic failure on rilpivirine with phenotypic resistance data lost susceptibility to rilpivirine. Of these, 28 were resistant to etravirine, 27 to efavirenz, and 14 to nevirapine.

Pharmacodynamics

Effects on Electrocardiogram

The effect of rilpivirine at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. Rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of rilpivirine were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady-state administration of rilpivirine 75 mg once daily and 300 mg once daily resulted in a mean C_{max} approximately 2.6-fold and 6.7-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 25 mg once daily dose of rilpivirine.

Pharmacokinetics

One EVIPLERA tablet is bioequivalent to one VIREAD tablet (300 mg) plus one EMTRIVA capsule (200 mg) plus one EDURANT tablet (25 mg) following single-dose administration to fed healthy subjects (N=34).

The separate pharmaceutical forms of tenofovir DF, emtricitabine and rilpivirine were used to determine the pharmacokinetics of tenofovir DF, emtricitabine and rilpivirine in HIV infected patients.

Tenofovir disoproxil fumarate: The pharmacokinetic properties of tenofovir DF are summarized in Table 1. Following oral administration of tenofovir DF, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over the range of 0.01 to 25 $\mu\text{g/mL}$. Approximately 70 to 80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir DF, the terminal elimination half-life of tenofovir is approximately 17 hours.

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 1. Following oral administration of emtricitabine 200 mg capsules, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is <4% and is independent of concentration over the range of 0.02 to 200 $\mu\text{g/mL}$. Following administration of radiolabelled emtricitabine approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine 200 mg capsules, the plasma emtricitabine half-life is approximately 10 hours.

Table 1. Single Dose Pharmacokinetic Parameters for Tenofovir and Emtricitabine in Adults¹

	Tenofovir	Emtricitabine
Fasted Oral Bioavailability (%)	25	93
Plasma Terminal Elimination Half-Life (hr)	17	10
C_{max} ($\mu\text{g/mL}$)	0.30 ± 0.09	1.8 ± 0.7^2
AUC ($\mu\text{g}\cdot\text{hr/mL}$)	2.29 ± 0.69	10.0 ± 3.1^2
CL/F (mL/min)	1043 ± 115	302 ± 94
CL _{renal} (mL/min)	243 ± 33	213 ± 89

1. Data presented as mean values.
2. Data presented as steady state values.

Rilpivirine: The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in adult antiretroviral treatment-naïve HIV-1 infected patients. Exposure to rilpivirine was generally lower in HIV-1 infected patients than in healthy subjects. After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4 to 5 hours. The mean C_{0h} and AUC_{24h} values in HIV-1 infected subjects were 0.080 ± 0.037 $\mu\text{g/mL}$ and 2.40 ± 1.03 $\mu\text{g}\cdot\text{hr/mL}$, respectively. The absolute bioavailability of RPV is unknown. Rilpivirine is approximately 99.7% bound to plasma proteins in vitro, primarily to albumin. In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome CYP3A system. The terminal elimination half life of rilpivirine is approximately 45 hours. After single dose oral administration of ^{14}C -rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.

Effect of food

Tenofovir disoproxil fumarate and emtricitabine: Compared to fasted administration, dosing of tenofovir DF and emtricitabine in combination with either a high fat meal or a light meal increased the AUC and C_{max} of tenofovir by approximately 40% and 14%, respectively, without affecting emtricitabine exposures.

Rilpivirine: The exposure to rilpivirine is approximately 40% lower when RPV was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high-fat, high-caloric meal (928 kcal). When RPV was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal.

Age, Gender and Ethnicity

Pharmacokinetic studies with EVIPLERA have not been fully evaluated in children (<18 years) or in the elderly (over 65 years) (see PRECAUTIONS).

Population pharmacokinetic analysis in HIV-1 infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years) evaluated.

No clinically important pharmacokinetic differences due to gender or ethnicity have been identified.

Patients with Impaired Renal Function

EVIPLERA is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min).

Tenofovir disoproxil fumarate and emtricitabine: Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir DF that cannot be achieved with the combination tablet (see PRECAUTIONS).

Rilpivirine: The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. Therefore, the impact of renal impairment on rilpivirine elimination is expected to be minimal. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Patients with Hepatic Impairment

The pharmacokinetics of EVIPLERA have not been studied in patients with hepatic impairment.

Tenofovir disoproxil fumarate and emtricitabine: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of emtricitabine have not been studied in patients with moderate to severe hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Rilpivirine: Rilpivirine is primarily metabolized and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. No rilpivirine dose adjustment is required in patients with mild or moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child Pugh score C).

Hepatitis B and/or hepatitis C virus co-infection

Pharmacokinetics of tenofovir DF and emtricitabine have not been fully evaluated in hepatitis B and/or C co-infected patients. Population pharmacokinetic analysis indicated that hepatitis B and/or C virus coinfection had no clinically relevant effect on the exposure to rilpivirine.

CLINICAL TRIALS

The data available to support the efficacy of EVIPLERA tablets include the available data for each individual agent, the data from clinical studies C209 and C215 where the three agents were used concurrently, and the demonstration of bioequivalence between EVIPLERA tablets and the three individual agents co-administered under fed conditions. No new clinical efficacy or safety studies have been conducted with the EVIPLERA tablet.

The efficacy of EVIPLERA is based on the analyses of 48 week data from two randomised, double-blind, controlled studies TMC278-C209 (C209) and TMC278-C215 (C215) in treatment naïve, HIV-1 infected patients (N = 1368). The studies are identical in design with the exception of the background regimen (BR). Patients were randomized in a 1:1 ratio to receive either rilpivirine 25 mg (N = 686) once daily or efavirenz 600 mg (N = 682) once daily in addition to a BR. In C209 (N = 690), the BR was tenofovir DF/emtricitabine. In C215 (N = 678), the BR consisted of 2 NRTIs: tenofovir DF/emtricitabine (60%, N = 406) or lamivudine/zidovudine (30%, N = 204) or abacavir plus lamivudine (10%, N = 68).

For patients who received tenofovir DF/emtricitabine (N = 1096) in C209 and C215, the mean age was 37 years (range 18 to 78), 78% were male, 62% were White, 24% were Black, and 11% were Asian. The mean baseline CD4 cell count was 265 cells/mm³ (range 1 to 888) and median baseline plasma HIV-1 RNA was 5 log₁₀ copies/mL (range 2 to 7).

Patients were stratified by baseline HIV-1 RNA. Fifty percent of patients had baseline viral loads > 100,000 copies/mL and 31% had CD4 cell counts < 200 cells/mm³. A subgroup analysis of the virologic response (<50 HIV-1 RNA copies/mL) at 48 weeks and virologic failure by baseline viral load (pooled data from the two Phase 3 clinical studies C209 and C215, for patients receiving the tenofovir DF/emtricitabine background regimen) is presented in Table 2.

Table 2 Virologic Outcome of Randomised Treatment of Studies C209 and C215 (Pooled Data for Patients Receiving Rilpivirine or Efavirenz in Combination with Tenofovir DF/Emtricitabine) at Week 48

	TDF/FTC + Rilpivirine N = 550	TDF/FTC + Efavirenz N = 546
Overall Response (HIV-1 RNA <50 copies/mL (TLOVR ^a))	83% (459/550)	82% (450/546)
By baseline viral load (copies/mL)		
≤ 100,000	90% (258/288)	85% (217/256)
> 100,000	77% (201/262)	80% (233/290)
Non-response		
Virological Failure (all patients)	10% (52/550)	4% (23/546)
By baseline viral load (copies/mL)		
≤ 100,000	4% (12/288)	2% (6/256)
> 100,000	15% (40/262)	6% (17/290)
Death	0	0.2% (1/546)
Discontinued due to adverse event (AE)	2% (12/550)	7% (39/546)
Discontinued for non-AE reason ^b	5% (27/550)	6% (33/546)

N= total number of patients per treatment arm.

a. ITT TLOVR = Intention to Treat Time to loss of virologic response.

b. e.g. loss to follow up, non-compliance, withdrew consent

Eighty-three percent of the patients in the rilpivirine arm and 82% of the patients in the efavirenz arm achieved plasma HIV-1 RNA <50 copies/mL by Week 48 (Table 2). The difference of response rate is -3% to 6% (95% confidence interval). Therefore, rilpivirine in combination with tenofovir DF/emtricitabine has been shown to be non-inferior in achieving HIV-1 RNA <50 copies/mL when compared to efavirenz in combination with tenofovir DF/emtricitabine.

For patients with baseline HIV-1 RNA ≤100,000 copies/mL, 90% and 85% of patients who received rilpivirine in combination with tenofovir DF/emtricitabine and efavirenz in combination with tenofovir DF/emtricitabine, respectively, achieved plasma HIV-1 RNA <50 copies/mL by Week 48 (TLOVR analysis) (Table 2). For subjects with baseline HIV-1 RNA >100,000 copies/mL, 77% and 80% of patients treated with rilpivirine in combination with tenofovir DF/emtricitabine and efavirenz in combination with tenofovir DF/emtricitabine, respectively, achieved plasma HIV-1 RNA <50 copies/mL.

Virologic outcomes were comparable in males and females in studies C209 and C215.

Based on the pooled data from the C209 and C215 trials at 48 weeks of treatment, the mean CD4 cell count increase from baseline was 193 cells/mm³ for rilpivirine plus tenofovir DF/emtricitabine-treated subjects and 182 cells/mm³ for efavirenz plus tenofovir DF/emtricitabine-treated subjects.

Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides are presented in Table 3. The mean changes from baseline were smaller in the rilpivirine arm versus the efavirenz arm. The impact of such findings has not been demonstrated.

Table 3 Lipid Values Reported in Subjects Receiving Rilpivirine or Efavirenz in Combination with Tenofovir DF/Emtricitabine in Studies C209 and C215

	Pooled Data from the C209 and C215 Trials			
	TDF/FTC + Rilpivirine N=550		TDF/FTC + Efavirenz N=546	
	Baseline	Week 48	Baseline	Week 48
	Mean (mg/dL)	Mean Change ^a (mg/dL)	Mean (mg/dL)	Mean Change ^a (mg/dL)
Total Cholesterol (fasted)	162	-0.4	161	26
HDL-cholesterol (fasted)	41	3	40	10
LDL-cholesterol (fasted)	97	-2	96	13
Triglycerides (fasted)	124	-12	132	12

a. The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 48 values.

INDICATIONS

EVIPLERA is indicated for the treatment of HIV infection in treatment-naïve adult patients with plasma HIV-1 RNA \leq 100,000 copies/mL at the start of therapy.

CONTRAINDICATIONS

EVIPLERA is contraindicated in patients with known hypersensitivity to any of the active substances or any other component of the tablets.

EVIPLERA must not be administered to children or adolescents under the age of 18 years.

EVIPLERA is a fixed-dose combination of tenofovir DF, emtricitabine and rilpivirine. EVIPLERA should not be administered concurrently with other medicinal products containing any of the same active components: VIREAD[®] (tenofovir DF), EMTRIVA[®] (emtricitabine), EDURANT[®] (rilpivirine), TRUVADA[®] (tenofovir DF / emtricitabine combination tablet), ATRIPLA[®] (tenofovir DF / emtricitabine / efavirenz combination tablet), or with medicinal products containing lamivudine or with HEPSERA[®] (adefovir dipivoxil).

EVIPLERA should not be co-administered with the following medicinal products, as significant decreases in rilpivirine plasma concentrations may occur (due to CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of EVIPLERA:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifabutin, rifampicin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone, except as a single dose treatment
- St John's wort (*Hypericum perforatum*).

PRECAUTIONS

General

Patients receiving EVIPLERA or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients should be advised that antiretroviral therapies, including EVIPLERA, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used. Patients should also be informed that EVIPLERA is not a cure for HIV infection.

Virologic failure and development of resistance

More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy. The observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz. More subjects treated with rilpivirine developed lamivudine/emtricitabine associated resistance compared to efavirenz (see PHARMACOLOGY and CLINICAL TRIALS).

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues including the tenofovir DF component of EVIPLERA, alone or in combination with other antiretrovirals, in the treatment of HIV infection. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with EVIPLERA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Renal Impairment

The emtricitabine and tenofovir DF components of EVIPLERA are primarily excreted by the kidneys; however, rilpivirine is not. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and Fanconi syndrome have been reported with the use of tenofovir DF in clinical practice.

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and, as clinically appropriate, during EVIPLERA therapy. Patients at risk for, or with a history of, renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA, should be routinely monitored for changes in serum creatinine and phosphorus.

EVIPLERA is not recommended for patients with moderate or severe renal impairment (CrCl <50 mL/min, including patients who require haemodialysis). Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir DF that cannot be achieved with the combination tablet.

EVIPLERA should be avoided with concurrent or recent use of a nephrotoxic agent.

Hepatic impairment

There is limited information regarding the use of rilpivirine in patients with mild or moderate hepatic impairment, resulting in unexpected variability in the available data. Rilpivirine has not been studied in patients with severe hepatic impairment (see Pharmacokinetics). EVIPLERA should be used with caution in patients with moderate to severe hepatic impairment (see Pharmacokinetics).

Bone Effects

Bone toxicity including a reduction in bone mineral density have been observed in tenofovir DF studies in three animal species. Clinically relevant bone abnormalities have not been seen in long term clinical studies (>3 years) with VIREAD. However, bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see ADVERSE EVENTS). If bone abnormalities are suspected during therapy then appropriate consultation should be obtained.

HIV and Hepatitis B Virus (HBV) Co-infection

Discontinuation of EVIPLERA therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to the emtricitabine and tenofovir DF components of EVIPLERA. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping EVIPLERA treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-hepatitis B therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the

measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tenofovir DF, emtricitabine and rilpivirine. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Impairment of Fertility

No reproductive toxicity studies have been conducted with tenofovir DF, emtricitabine and rilpivirine in combination.

Tenofovir disoproxil fumarate: Male and female rat fertility and mating performance or early embryonic development were unaffected by an oral tenofovir DF dose (600 mg/kg/day) that achieved systemic drug exposures that were in excess of the expected value in humans receiving the therapeutic dose (5-fold based on plasma AUC). There was, however, an alteration of the oestrous cycle in female rats.

Emtricitabine: Emtricitabine did not affect fertility in male rats or in female and male mice at respective approximate exposures (AUC) of 130 and 50 to 80 times the exposure in humans. The fertility of offspring was unaffected by treatment of mice from early gestation to the end of lactation (50 times the human exposure).

Rilpivirine: In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg/kg/day, a dose of rilpivirine that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

Use in Pregnancy

Pregnancy Category B3

There are no well controlled clinical studies of EVIPLERA in pregnant women. No embryofoetal development studies have been conducted with tenofovir DF, emtricitabine and rilpivirine in combination. Because animal reproductive studies are not always predictive of human response, EVIPLERA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Tenofovir disoproxil fumarate: Reproductive toxicity studies performed in rats and rabbits did not reveal any evidence of harm to the fetus due to tenofovir at respective exposures (AUC) of 4-13 and 66-fold the human exposure. Subcutaneous treatment of pregnant rhesus monkeys with a dose of 30 mg/kg/day of the tenofovir base during the last half of pregnancy resulted in reduced fetal serum phosphorus concentrations.

Emtricitabine: No evidence of embryofetal toxicity or teratogenicity was observed in mice or rabbits at respective emtricitabine exposures (AUC) of 50 and 130 fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in emtricitabine exposures (AUC) at least 33 times the clinical exposure was not associated with any adverse fetal effects.

Rilpivirine: Placental transfer of rilpivirine or its metabolites from dam to fetus was demonstrated in rats. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. There was no clinically relevant teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo fetal No Observed Adverse Effect Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg rilpivirine once daily.

Use in Lactation

Studies in rats have demonstrated that tenofovir and rilpivirine is excreted into milk.

It is not known whether tenofovir, emtricitabine or rilpivirine are excreted in human milk. Because of the potential for both HIV transmission and for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving EVIPLERA.

Animal Toxicology

Tenofovir disoproxil fumarate: Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Use in Children

EVIPLERA is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

Use in the Elderly

Clinical studies of tenofovir DF, emtricitabine and rilpivirine did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Caution should be exercised when prescribing EVIPLERA to the elderly, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Genotoxicity

No genotoxicity studies have been conducted with tenofovir DF, emtricitabine and rilpivirine in combination.

Tenofovir disoproxil fumarate was mutagenic in an in vitro mouse L5178Y lymphoma cell assay (tk locus) and in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes, but it was negative in *in vitro* bacterial assays for gene mutation and an *in vivo* mouse micronucleus test for chromosomal damage.

Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo*.

Rilpivirine has tested negative in the in vitro Ames reverse mutation assay, in vitro chromosomal aberration assay in human lymphocyte and in vitro clastogenicity mouse lymphoma assay, tested in the absence and presence of a metabolic activation system. Rilpivirine did not induce chromosomal damage in the in vivo micronucleus test in mice.

Mutagenicity

No carcinogenicity studies have been conducted with tenofovir DF, emtricitabine and rilpivirine in combination.

Tenofovir disoproxil fumarate: In a long-term carcinogenicity study conducted in mice with tenofovir DF there was a low incidence of duodenal tumours with the highest dose of 600 mg/kg/day. These were associated with a high incidence of duodenal mucosal hyperplasia, which was also observed with a dose of 300 mg/kg/day. These findings may be related to high local drug concentrations in the gastro-intestinal tract, likely to result in much higher exposure margins than that based on the AUC. At therapeutic doses the risk of these duodenal effects occurring in humans is likely to be low. The systemic drug exposure (AUC) with the 600 mg/kg/day dose was approximately 15 times the human exposure at the therapeutic dose of 300 mg/day. No tumourigenic response was observed in rats treated with doses of up to 300 mg/kg/day (5 times the human systemic exposure at the therapeutic dose based on AUC).

Emtricitabine: In long-term oral carcinogenicity studies conducted with emtricitabine, no drug-related increases in tumour incidence were found in mice at doses up to 750 mg/kg/day (32 times the human systemic exposure (AUC) at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (38 times the human systemic exposure at the therapeutic dose).

Rilpivirine: Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1,500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent specific, associated with liver enzyme induction. A similar mechanism does not exist in humans; hence, these tumors are not relevant for humans. The follicular cell findings are considered to be rat specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21 fold (mice) and 3 fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily).

Drug Interactions and Other Forms of Interactions

General

No drug interaction studies have been conducted using EVIPLERA tablets. As EVIPLERA contains tenofovir DF, emtricitabine and rilpivirine, any interactions that have been identified with these agents individually may occur with EVIPLERA.

Tenofovir and emtricitabine are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, co-administration of TRUVADA with drugs that are eliminated by active tubular secretion may increase serum concentrations of tenofovir, emtricitabine, and/or the co-administered drug. Drugs that decrease renal function may increase serum concentrations of tenofovir and/or emtricitabine.

Drugs Inducing or Inhibiting CYP3A Enzymes

Rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of rilpivirine.

Coadministration of rilpivirine and drugs that induce CYP3A resulted in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of EVIPLERA (see Table 5 for drugs studied). Other drugs inducing CYP3A enzymes include carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifapentine, dexamethasone, and St. John's wort (*Hypericum perforatum*) (see CONTRAINDICATIONS).

Coadministration of rilpivirine and drugs that inhibit CYP3A resulted in increased plasma concentrations of rilpivirine (see Table 5 for drugs studied).

Drugs Increasing Gastric pH

Coadministration of rilpivirine with drugs that increase gastric pH (such as proton pump inhibitors, H₂-receptor antagonists, and antacids) may decrease plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of EVIPLERA (see Table 5 for drugs studied) (see CONTRAINDICATIONS).

Didanosine

Concomitant dosing of tenofovir DF with didanosine buffered tablets or enteric-coated capsules significantly increase the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir DF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. Table 4 below, summarises the effects of tenofovir DF on the pharmacokinetics of didanosine.

As a result of this increased exposure, patients receiving EVIPLERA and didanosine should be carefully monitored for didanosine-associated adverse events, including pancreatitis, lactic acidosis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily. In adults weighing ≥60kg, the didanosine dose should be reduced to 250 mg daily when it is coadministered with EVIPLERA. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60

kg. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.

Table 4 Drug Interactions: Changes in Pharmacokinetic Parameters for Didanosine and Atazanavir in the Presence of Tenofovir DF

Co-administered Drug	Dose of Co-administered Drug (mg)	N	% Change of Co-administered Drug Pharmacokinetic Parameters ¹ (90% CI)		
			C _{max}	AUC	C _{min}
Didanosine ³ enteric-coated capsules	400 once / with or without food ²	26	↑ 48–64% (↑ 25–↑ 89)	↑ 48–60% (↑ 31–↑ 79)	NC
	250 once / Simultaneously with tenofovir DF, fasted ⁴	28	○	↑ 14 (0–↑ 31)	NC
	250 once / Simultaneously with tenofovir DF, fed ^{2, 4}	28	↓ 29 (↓ 39–↓ 18)	↓ 11 (↓ 23–↑ 2)	NC
Atazanavir sulfate ⁵	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/Ritonavir ⁶ 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5) ⁶	↓ 25 (↓ 42 to ↓ 3) ⁶	↓ 23 (↓ 46 to ↑ 10) ⁶

1. Increase = ↑; Decrease = ↓; No Effect = ○ ; NC = Not Calculated
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. See PRECAUTIONS regarding use of didanosine with tenofovir disoproxil fumarate.
4. Relative to 400 mg alone, fasted.
5. Reyataz Prescribing Information (Bristol-Myers Squibb)
6. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone (Reyataz March 2004 United States Package Insert)

Atazanavir:

Tenofovir DF decreases exposure to atazanavir and should only be administered with boosted atazanavir (atazanavir 300 mg/ritonavir 100 mg). No data are available to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with EVIPLERA. Table 4 summarises the effects of tenofovir DF on the pharmacokinetics of atazanavir.

QT Prolonging Drugs:

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and drugs that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, suprathreshold doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram. EVIPLERA should be used with caution when coadministered with a drug with a known risk of QTc prolongation.

Table 5 Established Significant ^a Drug Interactions

Concomitant Drug Class: Drug Name	Effect^b	Clinical Comment
Antiretroviral Agents:		
didanosine ^c	↑ didanosine	In patients weighing > 60 kg, the didanosine dose should be reduced to 250 mg if used concomitantly with EVIPLERA. Data are not adequate to support a specific recommendation for dosing in patients weighing < 60 kg. Patients receiving EVIPLERA and didanosine should be monitored closely for didanosine-associated adverse reactions e.g., pancreatitis, lactic acidosis. As didanosine is administered on an empty stomach, didanosine should be administered at least one hour before or two hours after EVIPLERA (which should be administered with a meal). For additional information, please consult the Videx/Videx EC (didanosine) product information.
atazanavir/ritonavir atazanavir	↑ tenofovir ^c ↓ atazanavir ^c	Tenofovir DF decreases exposure to atazanavir and should only be administered with boosted atazanavir (atazanavir 300 mg/ritonavir 100 mg). No data are available to support dosing recommendations for atazanavir or atazanavir/ritonavir in combination with EVIPLERA.
darunavir/ritonavir ^c	↑ rilpivirine	Concomitant use of EVIPLERA with darunavir/ritonavir may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EVIPLERA is coadministered with darunavir/ritonavir.
lopinavir/ritonavir ^c	↑ rilpivirine	No dose adjustment is required when EVIPLERA is coadministered with lopinavir/ritonavir.
Other Agents:		
Azole Antifungal Agents: ketoconazole ^c	↑ rilpivirine ↓ ketoconazole	Concomitant use of EVIPLERA with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). No dose adjustment is required when EVIPLERA is coadministered with azole antifungal agents.
Antimycobacterials: rifabutin ^c rifampin ^c	↓ rilpivirine	EVIPLERA should not be used in combination with rifabutin, or rifampin as coadministration may cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of EVIPLERA.
Proton Pump Inhibitors: omeprazole ^c	↓ rilpivirine ↓ omeprazole	EVIPLERA should not be used in combination with proton pump inhibitors as coadministration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). This may result in loss of therapeutic effect of EVIPLERA.

Concomitant Drug Class: Drug Name	Effect^b	Clinical Comment
H₂-Receptor Antagonists: famotidine ^c	↔ □ GAE KGC [←] (famotidine taken 12 hours before rilpivirine) ↓ rilpivirine (famotidine taken 2 hours before rilpivirine) ↔ rilpivirine (famotidine taken 4 hours after rilpivirine)	The combination of EVIPLERA and H ₂ -receptor antagonists should be used with caution as coadministration may cause significant decreases in rilpivirine plasma concentrations (increase in gastric pH). H ₂ -receptor antagonists should only be administered at least 12 hours before or at least 4 hours after EVIPLERA.
Narcotic Analgesics: methadone	↓ R (–) methadone ↓ S (+) methadone	No dose adjustments are required when initiating coadministration of methadone with EVIPLERA. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.

- a. This table is not all inclusive.
b. ↑ = increase, ↓ = decrease, ↔ = no effect
c. This interaction study has been performed with a dose (150 mg of rilpivirine) higher than the recommended dose for rilpivirine assessing the maximal effect on the coadministered drug. The dosing recommendation is applicable to the recommended dose of rilpivirine 25 mg once daily.

Interactions with other medicinal products

Caution should be given to prescribing rilpivirine with medicinal products that may reduce the exposure to rilpivirine. For information on interactions with other medicinal products (see Table 5 above).

Drugs Without Clinically Significant Interactions

The drug interactions described are based on studies conducted with tenofovir DF, emtricitabine, or rilpivirine as individual agents.

Tenofovir disoproxil fumarate: No clinically significant drug interactions have been observed between tenofovir DF and abacavir, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, or saquinavir/ritonavir.

Emtricitabine: No clinically significant drug interactions have been observed between emtricitabine and indinavir, zidovudine, stavudine, famciclovir, or tenofovir DF.

Rilpivirine: No clinically significant drug interactions have been observed between rilpivirine and acetaminophen, atorvastatin, ethinylestradiol, norethindrone, sildenafil, didanosine, or tenofovir DF.

Effects on ability to drive and use machines

No studies on the effects of EVIPLERA on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with tenofovir DF, emtricitabine, and rilpivirine.

ADVERSE EFFECTS

As EVIPLERA contains tenofovir DF, emtricitabine and rilpivirine, adverse events associated with these individual antiretroviral agents may be expected to occur with the fixed combination tablet.

For additional safety information about VIREAD (tenofovir DF), EMTRIVA (emtricitabine) or EDURANT (rilpivirine) in combination with other antiretroviral agents, consult the Product Information for these products.

CLINICAL TRIALS

Tenofovir disoproxil fumarate + Emtricitabine + Rilpivirine:

Studies C209 and C215: - *Treatment Emergent Adverse Reactions:* Studies C209 and C215 were randomised, double-blind, active-controlled studies in which 80% of antiretroviral-naive subjects received tenofovir DF + emtricitabine administered in combination either with rilpivirine (N=550) or with efavirenz (N=546) [see CLINICAL TRIALS]. The median duration of exposure for subjects in either treatment arm was 56 weeks. Adverse reactions observed in these studies were generally consistent with those seen in previous studies of the individual components (Table 6).

The most common adverse events (incidence 3%, Grades 2-4) that occurred in patients receiving tenofovir DF, emtricitabine, and rilpivirine in clinical trials C209 and C215 were depression and diarrhoea.

Table 6 Selected Treatment-Emergent Adverse Reactions^a (Grades 2–4) Reported in >2% of Subjects Receiving Rilpivirine or Efavirenz in Combination with Tenofovir DF/Emtricitabine DF in Studies C209 and C215

	TDF/FTC + Rilpivirine	TDF/FTC + Efavirenz
	N=550	N=546
Gastrointestinal Disorder		
Diarrhoea ^b	4%	3%
Nausea	1%	3%
General Disorders and Administration Site Condition		
Fatigue	1%	2%
Infections and Infestations		
Upper respiratory tract infection ^b	2%	2%
Nervous System Disorders		
Dizziness	1%	7%
Headache	3%	3%
Psychiatric Disorders		
Abnormal dreams	1%	3%
Anxiety	1%	3%
Depression	4%	2%
Insomnia	3%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	2%	7%

- a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
b. Adverse reactions not associated with rilpivirine.

Laboratory Abnormalities: Laboratory abnormalities observed in studies C209 and C215 were generally consistent with those seen in other studies of the individual components (Table 7).

Table 7 Significant Laboratory Abnormalities (Grades 3-4) Reported in ≥1% of Subjects Who Received Rilpivirine or Efavirenz in Combination with Tenofovir DF/Emtricitabine in Studies C209 and C215

	TDF/FTC + Rilpivirine	TDF/FTC + Efavirenz
	N=549	N=536
Pancreatic Amylase (>2 ULN ^a)	3%	4%
Lipase (>3 ULN)	<1%	1%
AST (>5 ULN)	2%	3%
ALT (>5 ULN)	1%	3%
Total Cholesterol (fasted) (>300 mg/dL)	<1%	2%
LDL-Cholesterol (fasted) (>191 mg/dL)	<1%	2%
Triglycerides (fasted) (>751 mg/dL)	<1%	2%

a. ULN=Upper limit of normal value.

Rilpivirine was associated with fewer neurological and psychiatric adverse reactions than efavirenz in subjects who received emtricitabine/tenofovir DF in Studies C209 and C215. In addition to the adverse events in Studies C209 and C215 (Table 6), the following adverse events were observed in clinical studies of tenofovir DF, emtricitabine and rilpivirine in combination with other antiretroviral agents.

Tenofovir disoproxil fumarate: More than 12,000 patients have been treated with VIREAD alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase I-III clinical trials and expanded access studies. A total of 1,544 patients have received VIREAD 300 mg once daily in Phase I-III clinical trials; over 11,000 patients have received VIREAD in expanded access studies.

The most common adverse events that occurred in patients receiving VIREAD with other antiretroviral agents in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhoea, vomiting and flatulence.

Emtricitabine: More than 2000 adult patients with HIV infection have been treated with EMTRIVA alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase I-III clinical trials.

Assessment of adverse reactions is based on data from studies 301A and 303 in which 571 treatment naïve (301A) and 440 treatment experienced (303) patients received EMTRIVA 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical trials were headache, diarrhoea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the EMTRIVA treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

In addition to the adverse reactions reported in adults, anaemia has been reported commonly and hyperpigmentation very commonly, in paediatric patients.

Rilpivirine: Adverse reactions that occurred in up to 2% of patients receiving rilpivirine with other antiretroviral agents in clinical trials include decreased appetite, sleep disorders, depressed mood, somnolence, abdominal pain, vomiting, and abdominal discomfort.

Adrenal Function: In the pooled Phase 3 trials of C209 and C215, in patients treated with rilpivirine plus any of the allowed background regimen (N=686), at Week 48, the overall mean change from baseline in basal cortisol showed a decrease of -13.1 nmol/L in the rilpivirine group, and an increase of +9.0 nmol/L in the efavirenz group. At Week 48, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the rilpivirine group ($+16.5 \pm 6.14$ nmol/L) than in the efavirenz group ($+58.1 \pm 6.66$ nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 48 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. Effects on adrenal function were comparable by background N(t)RTIs.

Serum Creatinine: In the pooled Phase 3 trials of C209 and C215 trials in patients treated with rilpivirine plus any of the allowed background regimen (N=686), increases in serum creatinine occurred within the first four weeks of treatment and remained stable through 48 weeks. A mean change of 0.09 mg/dL (range: -0.20 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. In patients who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. These changes are not considered to be clinically relevant and no subject discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

Patients coinfecting with hepatitis B and/or hepatitis C virus: In patients coinfecting with hepatitis B or C virus receiving rilpivirine in studies C209 and C215, the incidence of hepatic enzyme elevation was higher than in patients receiving rilpivirine who were not coinfecting. The same increase was also observed in the efavirenz arm. The pharmacokinetic exposure of rilpivirine in coinfecting patients was comparable to that in patients without coinfection.

POST MARKETING SURVEILLANCE

In addition to adverse events reported from clinical trials, the following events have been reported in post marketing surveillance. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Tenofovir disoproxil fumarate

IMMUNE SYSTEM DISORDERS

Allergic reaction (including angioedema), immune reconstitution syndrome

METABOLISM AND NUTRITION DISORDERS

Hypokalaemia, hypophosphataemia, lactic acidosis

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Dyspnoea

GASTROINTESTINAL DISORDERS

Increased amylase, abdominal pain, pancreatitis

HEPATOBIILIARY DISORDERS

Hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT, gamma GT)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Rash

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Rhabdomyolysis, muscular weakness, myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures)

RENAL AND URINARY DISORDERS

Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal renal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Asthaenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy, hypophosphataemia. These events are not considered to be causally associated with tenofovir DF therapy in the absence of proximal renal tubulopathy.

Exacerbations of Hepatitis after Discontinuation of Treatment

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of treatment (see PRECAUTIONS).

Emtricitabine

IMMUNE SYSTEM DISORDERS

Immune reconstitution syndrome

DOSAGE AND ADMINISTRATION

Adults: The recommended dose of EVIPLERA is one tablet once daily taken orally with a meal.

Renal impairment: EVIPLERA is not recommended for use in patients with moderate or severe renal impairment (Creatinine Clearance (CrCl) < 50 mL/min). Patients with moderate or severe renal impairment require dose interval adjustments of tenofovir DF and emtricitabine that cannot be achieved with the combination tablet (see PRECAUTIONS).

When discontinuation of EVIPLERA is necessary due to one of the components, or where dose modification is necessary, separate preparations of tenofovir DF, emtricitabine and rilpivirine should be used. Please refer to the product information for these products.

OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with EVIPLERA consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient.

Tenofovir disoproxil fumarate: Clinical experience of doses higher than the therapeutic dose of VIREAD 300 mg is available from two studies. In one study, intravenous tenofovir, equivalent to 16.7 mg/kg/day of tenofovir DF, was administered daily for 7 days. In the second study, 600 mg of tenofovir DF was administered to patients orally for 28 days. No unexpected or severe adverse reactions were reported in either study. The effects of higher doses are not known.

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour haemodialysis session removed approximately 10% of the administered tenofovir dose.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported. The effects of higher doses are not known.

Haemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Rilpivirine: There is no specific antidote for overdose with rilpivirine. Human experience of overdose with rilpivirine is limited. If indicated, elimination of unabsorbed active substance may be achieved by gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

PRESENTATION AND STORAGE CONDITIONS

EVIPLERA is available as tablets. Each tablet contains 300 mg tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil), 200 mg emtricitabine and 27.5 mg rilpivirine hydrochloride (which is equivalent to 25 mg rilpivirine). The tablets are film-coated, capsule shaped and purplish-pink in colour. Each tablet is debossed with 'GSI' on one side and plain on the other side.

EVIPLERA is supplied in high density polyethylene (HDPE) bottles containing 30 tablets and a desiccant (silica gel canister or sachet), polyester coil and is closed with a child resistant closure.

EVIPLERA should be stored below 25 °C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE DRUG

S4

DATE OF TGA APPROVAL: 23 January 2012

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