EU Risk Management Plan for
Eviplera®
(Emtricitabine/Rilpivirine/Tenofovir disoproxil fumarate)

EU Risk Management Plan for Eviplera® (Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate)

RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
17.0	08 May 2025	24 Nov 2025

Rationale for submitting an updated RMP:

The Risk Management Plan has been updated to remove the following:

- Important identified risks:
  - Renal toxicity (TDF)
  - Bone events due to proximal renal tubulopathy/loss of bone mineral density (BMD)
- Missing information:
  - Safety in patients with renal impairment
  - Safety in pregnancy
  - Safety in lactation
- The additional pharmacovigilance activity of “monitoring of reversibility of renal tubulopathy in clinical trials”
- Targeted questionnaires related to bone and renal risks corresponding to important identified risks and missing information.
- The category 3 additional pharmacovigilance activity of the Antiretroviral pregnancy register.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part I Product Overview	N/A	None.
Part II Safety Specification	Section Part II: Module SI: Epidemiology of the indication and target populations(s)	Epidemiology information updated.
	Section Part II: Module SII: Non-clinical part of the safety specification	None.
	Section Part II: Module SIII: Clinical trial exposure	None.
	Section Part II: Module SIV: Populations not studied in clinical trials	Information updated.
	Section Part II: Module SV: Postauthorization experience	Prescription and Post-authorization exposure data updated.
	Section Part II: Module SVI: Additional EU requirements for the safety specification	None.
	Section Part II: Module SVII: Identified and potential risks	Updated list of safety concerns. Further updated to remove the missing information "Safety in pregnancy" with rationale for removal. Update to reflect the removal of "safety in lactation" as missing information.
	Section Part II: Module SVIII: Summary of the safety concerns	List of safety concerns revised to align with Section Part II: Module SVII.
Part III Pharmacovigilance Plan		Updated to remove "Monitoring of reversibility of renal tubulopathy in clinical trials" from additional pharmacovigilance activities. Further updated to remove targeted questionnaires for bone and renal events and to remove the additional pharmacovigilance activity of the Antiretroviral Pregnancy Register (APR).
Part IV Plan for post-authorization efficacy studies		None.

Part	Module/Annex	Significant changes to RMP
Part V Risk Minimization Measures		Updated list of safety concerns to align with Part II Module SVII. Further updated to reflect the removal of the missing information "Safety in pregnancy" and the antiretroviral pregnancy register as an additional pharmacovigilance activity Removal of "safety in lactation" as missing information.
Part VI Summary of RMP		Updated to reflect changes in Parts II, III, and V. Further updated to reflect the removal of the missing information "Safety in pregnancy" and the antiretroviral pregnancy register as an additional pharmacovigilance activity. Removal of "safety in lactation" as missing information.
Part VII Annexes		Annexes 2, 3, and 8: updated to reflect the changes in the RMP document. Annexes 2, 3, 4 and 8 were further updated to reflect the removal of the missing information "Safety in pregnancy" and the antiretroviral pregnancy register as an additional pharmacovigilance activity. Annex 8 was updated to reflect the removal of "safety in lactation" as missing information.

Other RMP versions under evaluation:

There are no other EU-RMP versions under evaluation.

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
15.0	EMEA/H/C/002312/IB/0105	05 June 2020

QPPV name:	Rainer Heissing
QPPV signature:	The RMP has been reviewed and approved by the QPPV and the electronic signature is on file.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTG	AIDS Clinical Trial Group
ACTH	adrenocorticotropic hormone
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®)
AUC	area under the plasma concentration-time curve
BMD	bone mineral density
BUN	blood urea nitrogen
CCDS	company core data sheet
CD4	cluster of differentiation (antigenic marker on helper/inducer T cells)
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
CL_{cr}	creatinine clearance
CPT	Child-Pugh-Turcotte classification
CYP	cytochrome P450
dATP	deoxyadenosine triphosphate
ddI	Didanosine
DDI	drug-drug interaction
DEXA	dual energy X-ray absorptiometry
DF	disoproxil fumarate
DHHS	Department of Health and Human Services
DLP	data lock point
DNA	deoxyribonucleic acid
DRV	Darunavir
DTG	Dolutegravir
DUS	Drug Utilization Study
EACS	European AIDS Clinical Society
ECDC	European Center for Disease Prevention and Control
EEA	European Economic Area
EFV	Efavirenz
eGFR	estimated glomerular filtration rate

EMA	European Medicines Agency
EPA	emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Eviplera®)
EPAR	European Public Assessment Report
EU	European Union
EU-RMP	European Union Risk Management Plan
EVG	elvitegravir
FDA	Food and Drug Administration (US)
FTC	emtricitabine (Emtriva®)
GFR	glomerular filtration rate
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV (HIV-1)	human immunodeficiency virus (type 1)
IDU	injection drug use
INN	international nonproprietary name
INSTI	integrase strand-transfer inhibitor
LPV	Lopinavir
MAH	marketing authorization holder
MITOC	European collaboration on mitochondrial toxicity in children and NRTI exposure during pregnancy
MSM	men who have sex with men
N/A	not applicable
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
ODE	emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey®)
PASS	post-authorization safety study
PBRER	periodic benefit-risk evaluation report
P-gp	P-glycoprotein
PK	Pharmacokinetic
PI	protease inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
PRT	Proximal renal tubulopathy
PSUR	periodic safety update report
PYFU	person-years of follow up
QD	quaque die (once daily)
QPPV	qualified person for pharmacovigilance
QTc	corrected QT interval
RMP	Risk Management Plan
RNA	ribonucleic acid
RPV	rilpivirine (as hydrochloride, also known as TMC278)

RT	reverse transcriptase
SmPC	Summary of Product Characteristics
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
STR	single tablet regimen
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)
TdP	Torsade de Pointes
TFV	Tenofovir
TQT	thorough QT
UDS	unscheduled DNA synthesis assay
UDP-GT	uridine diphospho-glucuronosyltransferase
UK	United Kingdom
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV and AIDS
UNODC	United Nations Office on Drugs and Crime
US	United States
VF	virologic failure
WHO	World Health Organisation

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (TDF)
Pharmaco-therapeutic group(s) (ATC Code):	Antivirals for the treatment of HIV infections, combinations (J05AR08)
Marketing Authorization Holder:	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Eviplera
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Emtricitabine: nucleoside reverse transcriptase inhibitor (NRTI) Rilpivirine (as hydrochloride): nonnucleoside reverse transcriptase inhibitor (NNRTI) Tenofovir disoproxil fumarate: nucleotide reverse transcriptase inhibitor (NtRTI)
	Summary of mode of action Emtricitabine (FTC) is a nucleoside analogue of 2'-deoxycytidine. Intracellularly, FTC is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, the active metabolite, which competitively inhibits HIV reverse transcriptase, resulting in DNA chain termination. Rilpivirine (as hydrochloride) is a NNRTI active against wild type and NNRTI resistant human immunodeficiency virus 1 (HIV 1). Rilpivirine binds directly to viral reverse transcriptase (RT) and blocks the ribonucleic acid (RNA) dependent and deoxyribonucleic acid (DNA) dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. Tenofovir disoproxil fumarate (TDF), an oral prodrug of tenofovir, is an NtRTI. Following absorption, TDF is rapidly converted to tenofovir, which is metabolized intracellularly to the active metabolite, tenofovir diphosphate. Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxyadenosine triphosphate, dATP) and, after incorporation into DNA, by DNA chain termination.
	Important information about its composition None
Hyperlink to the Product Information	Eviplera Summary of Product Characteristics (SmPC)

Indication(s) in the EEA	Current: Treatment of adults infected with HIV-1 without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV-1 RNA copies/mL. As with other antiretroviral medicinal products, genotypic resistance testing and/or historical resistance data should guide the use of Eviplera.
	Proposed: Not applicable
Dosage in the EEA	Current: Adults: The recommended dose of Eviplera is one tablet, taken orally, once daily. Eviplera must be taken with food.
	Proposed: Not Applicable.
Pharmaceutical form(s) and strengths	Current: Film coated tablet containing 200 mg emtricitabine, 25 mg rilpivirine and 300 mg tenofovir DF.
	Proposed: Not applicable.
Is/Will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI- EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. HIV Infection

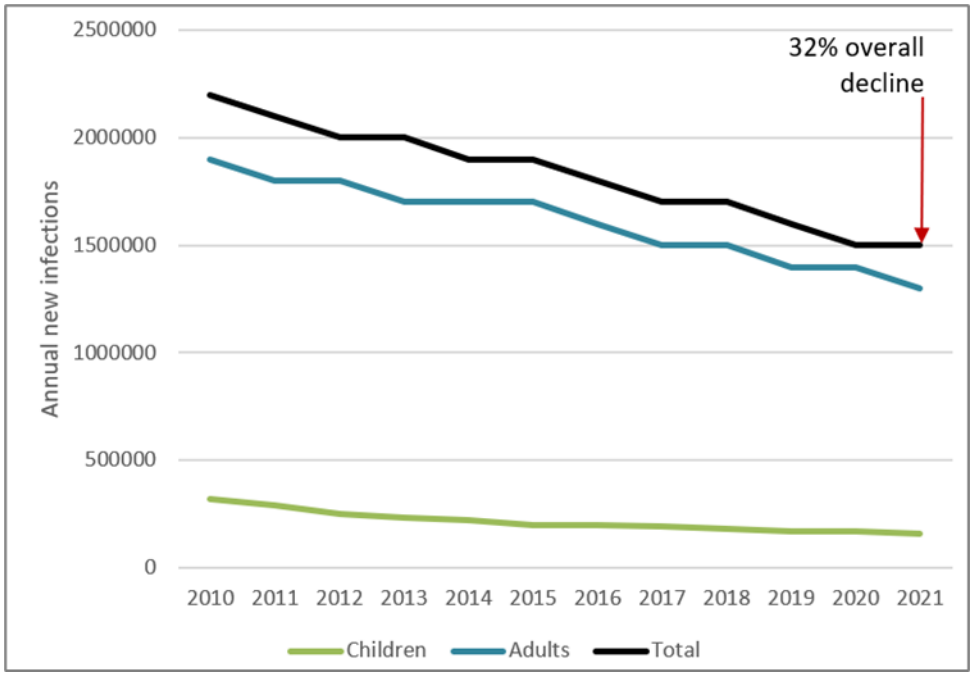
SI.1.1. Incidence

The estimated number of people (adults and children) acquiring HIV infection in 2021 was 1.5 million (95% confidence interval [CI]: 1.1 million- 2.0 million), resulting in a 32% overall decline since 2010 (Table 1, Figure 1) {HIV infections 2022b}. In 2021, the estimated number of adults acquiring HIV infection was 1.3 million (95% CI: 990,000-1.8 million) {New HIV infections 2022a}. Among children (<15 years old), the number of new infections in 2021 was estimated to be 160,000 (95% CI: 110,000-230,000) {New HIV infections 2022b} (Figure SI.1).

Considerable variations of HIV incidence and trends exist by region and within countries due to differences in structural and societal determinants across the globe. The region with the highest number of incident HIV cases in 2021 was Eastern and Southern Africa (670,000 [95% CI: 530,000-900,000]), followed by Asia and the Pacific (260,000 [95% CI: 190,000-360,000]). Notable declines in the number of new HIV infections overall from 2010 to 2021 have been observed in Eastern and Southern Africa (44% decrease since 2010), the Caribbean (28%), Western and Central Africa (43%), Western and Central Europe and North America (16%), and Asia and the Pacific (21%) {HIV infections 2022b}.

Nonetheless, HIV incidence continues to increase in some regions, with new infections in Eastern Europe and Central Asia increasing 48% between 2010 and 2021, largely due to transmission among people who inject drug (PWID) and structural barriers to HIV prevention and treatment programs {UNAIDS AidsInfo 2022b} {HIV infections 2022b} {HIV Infections 2022c}. Moreover, PrEP access and HIV prevention services are not uniform {HIV Infections 2022a}. The Middle East and North Africa and Latin America regions have also not experienced a significant decrease in the number of new infections over time, where stigma against those living with HIV and lack of resources for HIV prevention and treatment programs are major barriers to preventing infection and anti-retroviral therapy (ART) access, particularly among men who have sex with men (MSM), transgender women, sex workers, and sexual partners of these key populations {UNAIDS AidsInfo 2022b}. Globally, disproportionately higher proportions of new infections occur among PWID (10%), sex workers (12%), MSM (21%), and transgender women (2%).

Figure SI.1. Annual number of new HIV infections globally from 2010 to 2021



Sources: {New HIV infections 2022a, New HIV infections 2022b} {infections 2022f} {HIV infections 2022b}

SI.1.2. Prevalence

Approximately 36.7 million adults and 1.7 million children were living with HIV globally at the end of 2021 (total: 38.4 million; 95% CI: 33.9-43.8 million) (Table 1) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2022}. An estimated 0.6% (95% CI: 0.6-0.7%) of adults (15 years and above) worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions {UNAIDS AidsInfo 2022c}.

The Eastern and Southern Africa region is most severely affected, with an estimated 20.6 million (95% CI: 18.9-23.0 million) people living with HIV infection in 2021, accounting for 54% of people living with HIV worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2022}. The region with the second highest number of people living HIV is Asia and the Pacific (6.0 million [95% CI: 4.9-7.2 million]), followed by Western and Central Africa (5.0 million [95% CI: 4.5 5.6 million]) {UNAIDS AidsInfo 2022e}. In Eastern and Southern Africa and Western and Central Africa, which are referred to collectively as Sub-Saharan Africa, prevalence is high among key populations including MSM, sex workers, PWID, and sexual partners of these groups. After Sub-Saharan Africa and Asia and the Pacific, the regions most heavily affected are the Caribbean, Eastern Europe and Central Asia, and Latin America where 0.4 1.0% of adults were living with HIV in 2021{UNAIDS AidsInfo 2022c}. Eastern Europe and Central Asia is the only region where HIV prevalence has increased since 2010, reaching an estimated 1.6 million in 2020 (95% CI: 1.5-1.8 million), resulting largely from a surge of infections among PWID and their sexual partners {UNAIDS 2021}. In contrast, estimated regional prevalence is lower in Western and Central Europe and North America (0.3% [95% CI: 0.2-0.3]) in adults){UNAIDS AidsInfo 2022c}. In this region, unprotected sex between men continues to be the main route of HIV transmission, although more than 81% of people living with HIV are

accessing ART. In Western and Central Europe, stigma and discrimination within the health-care system persist as significant barriers to accessing HIV treatment among MSM, in addition to sex workers and PWIDs.{UNAIDS AidsInfo 2022c}

Table SI.1. Regional Prevalent and Incident Cases of HIV Infection in 2021

	Incident Cases (n; 95% CI)		Prevalent Cases (n; 95% CI)	
	Overall	**Adults[a]**	**Overall**	**Adults[a]**
Asia and Pacific	260,000 (190,000-360,000)	250,000 (180,000-350,000)	6 million (4.9-7.2 million)	5. 9 million (4.8-7.1 million)
Caribbean	14,000 (9,500-18,000)	13,000 (9000-17,000)	330,000 (290,000-380,000)	320,000 (280,000-370,000)
Eastern and Southern Africa	670,000 (530,000-900,000)	590,000 (460,000-790,000)	20,6 million (18.9-23 million)	19,6 million (17.9-21.8 million)
Eastern Europe and Central Asia	160,000 (130, 000-180, 000)	150,000 (130,000-180,000)	1,800,000 (1.7-2.0 million)	1,8 million (1.6-2.0 million)
Latin America	110,000 (68, 000-150, 000)	100,000 (65,000-150,000)	2,2 million (1.5-2.8 million)	2,1 million (1.5-2.7 million)
Middle East and North Africa	14,000 (11,000-18, 000)	12,000 (9800-16,000)	180,000 (150,000-210, 000)	170,000 (150,000-200,000)
Western and Central Africa	190,000 (140, 000-270, 000)	140,000 (90,000-210,000)	5 million (4.5-5.6 million)	4.5 million (4.1-5.2 million)
Western and Central Europe and North America	63,000 (51, 000-76, 000)	63,000 (51,000-76,000)	2.3 million (1.9-2.6 million)	2.3 million (1.9-2.6 million)
Total [b]	1,5 million (1.1-2 million)	1.3 million (990,000-1.8 million)	38.4 million (33.9-43.8 million)	36.7 million (32.3-41.9 million)

a Aged 15 years and older.
b Numbers in the columns may not add up to match the totals exactly due to the effect of rounding.
Source: {UNAIDS AidsInfo 2022d, UNAIDS AidsInfo 2022e}, {infections 2022f}, {New HIV infections 2022a}

SI.1.3. Demographics of the HIV Population

SI.1.3.1. HIV infection in Children

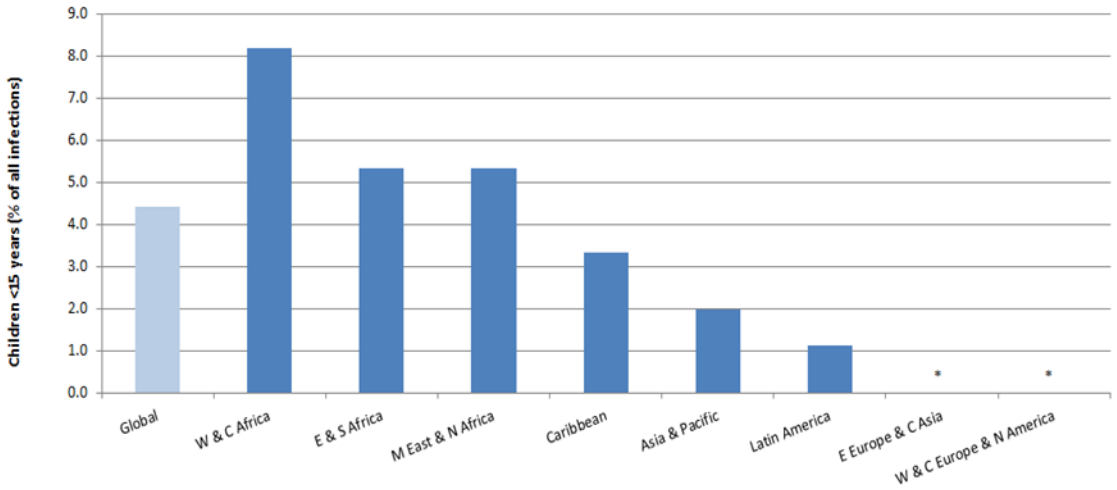
Worldwide, 1.7 million (95% CI: 1.3-2.1 million) children (<15 years of age) were living with HIV in 2021, accounting for a proportion of existing infections in Western and Central Africa (8.2%) and Eastern and Southern Africa (5.3%) (Figure 3) {UNAIDS AidsInfo 2022f} {UNAIDS AidsInfo 2022e}. Estimates of prevalence among children were unavailable for 2021 in Eastern Europe and Central Asia, Western and Central Europe, and North America regions.

Mother-to-child transmission is the main route of infection among children, by which a woman infected with HIV passes HIV to her child during pregnancy, childbirth, or breast milk. If the mother has access to ART during pregnancy, delivery, and breastfeeding, the risk of mother-to-child transmission reduces to 5% or less {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. Expansions in ART and infant feeding based prevention services

are primarily responsible for the observed declines in the number of newly infected children, which declined by 52% from 2010 to 2021 (Figure 1). Approximately 50% of all children who acquired HIV infection in 2020 were living in Eastern and Southern Africa, followed by Western and Central Africa (34%), Asia and Pacific (9%), Latin America (2%), Middle East and North Africa (<1%), and Caribbean (<1%) {UNAIDS AidsInfo 2021}.

Reductions in HIV incidence among children since 2010 have been observed in Eastern and Southern Africa, Caribbean, West and Central Africa, Latin America, and Asia and Pacific {UNAIDS AidsInfo 2021}. However, the Middle East and North Africa region has yet to experience a significant reduction in the number of children infected. This is likely attributable to the rates of mother-to-child transmission remaining high in the region (30% in 2019) due to low coverage of services for prevention of vertical transmission {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020}.

Figure SI.2. Proportion of Individuals Living with HIV Aged <15 years of age by Geographical Region in 2020



* Data on individuals infected with HIV aged <15 years old not available for Eastern Europe & Central Asia and Western & Central Europe and North America.
Source: {UNAIDS AidsInfo 2022e} {UNAIDS AidsInfo 2022f}

SI.1.3.2. The aging population of PWH

There is evidence to suggest that the life expectancy of HIV patients is approaching that of HIV-negative persons, if diagnosis and treatment occur at an early enough stage and patients maintain adherence to treatment {Nakagawa 2013}, though there is still variation by region and gender {Wandeler 2016}, {Teeraananchai 2017}. With increased life expectancy, the mean age of HIV patients continues to increase, and HIV is more prevalent among those who are older, particularly in countries where effective therapies were available earlier {Nakagawa 2013} {Wing 2016}. Worldwide, between 1995 and 2013, prevalence rates among those aged 50 years and older have gradually increased over time; and the proportion of those living with HIV who are above the age of 50 ranged from 10% (in low- and middle-income countries) to 30% (in high

income countries) {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017},{Mahy 2014}. In 2021, 8,400,000 (22%) of the people living with HIV globally were aged 50 years or over, up from 3,500,000 (11%) in 2010. UNAIDS reports that this trend is largely due to the success of ART, decreases in HIV incidence among adults below the age of 50 years, and those above 50 years of age having similar risk behaviors as those who are younger{UNAIDS 2013}.

SI.1.3.3. HIV Infection by Gender

Worldwide, males comprised approximately 51% of total new infections (all ages) in 2021 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2022}. From 2010 to 2021, the annual number of new HIV infections declined by 31% among males and 35% among females {infections 2022d, infections 2022e}.

However, differences in incidence by gender vary by region and age group, particularly in lower- and middle-income countries, where societal gender inequalities, differential access to services, and sexual violence contribute to increased infection risk {UNAIDS AidsInfo 2022b}. Women account for 64% of prevalent adult infections in Western and Central Africa, 64% in Eastern and Southern Africa, 50% in the Caribbean, 35% in Eastern Europe and Central Asia, 37% in Asia and Pacific, 39% in the Middle East and North Africa, 30% in Latin America, and 24% in Western and Central Europe and North America{HIV Infections 2022c}. Among young women (aged 15 to 24 years), incident infections reduced by 40% between 2010 and 2021, however, adolescent girls and young women still accounted for 17% of new adult HIV infections in 2021 and are globally twice as likely to become infected compared to men{infections 2022c, infections 2022f}. In 2021, there were 250,000 (95% CI 150,000-360,000) new HIV infections among adolescents and young women globally, 83% of which occurred in Sub-Saharan Africa. The annual incidence among women aged 15-24 years in Southern and East Africa was 3.54 per 1,000, compared to 1.42 in the whole population. Similarly, incidence was 0.67 per 1,000 young women in West and Central Africa, compared to 0.32 in the whole population{infections 2022a, infections 2022b}.

SI.1.4. Main Existing Treatment Options

For ART-naïve HIV-1 patients, current treatment guidelines in the EU favor initial therapy with one of the following drug combinations:

1. Two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus an unboosted integrase strand transfer inhibitor (INSTI) (dolutegravir [DTG] or bictegravir [BIC]) as the 3rd agent

2. One NRTI (3TC [lamivudine] or FTC [emtricitabine]) plus an INSTI (DTG)

3. Two NRTIs (tenofovir alafenamide [TAF] and FTC or tenofovir disoproxil fumarate [TDF] and XTC) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), doravirine (DOR) {European Aids Clinical Society (EACS) 2021}

In the current US treatment guidelines, the following are recommended regimens for most ART-naive patients{Panel on Antiretroviral Guidelines for Adults and Adolescents 2022}:

- INSTI-Based Regimens:
- BIC/TAF/ FTC
- DTG /abacavir/3TC—only for patients who are HLA-B*5701 negative
- DTG plus TDF/FTC or TAF/FTC
- DTG/3TC

For PWH and a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before the start of ART. When initiation takes place before the result is available, a boosted darunavir (DRV) plus (TAF or TDF) plus XTC should be used {Panel on Antiretroviral Guidelines for Adults and Adolescents 2022}.

While current combinations of ART for the treatment of HIV-1 infection are efficacious and well tolerated, these agents need to be taken every day to minimize the emergence of drug resistant variants. As such, there remains a significant medical need for ART that can be administered less frequently (i.e., long-acting drug products), thereby providing an alternative treatment option for PWH. Currently cabotegravir/rilpivirine is the only long-acting ART regimen approved for the treatment of HIV-1 infection, available as monthly or 2-monthly therapy {Panel on Antiretroviral Guidelines for Adults and Adolescents 2022}.

SI.1.5. Natural History of the Indicated Condition including Mortality and Morbidity

Untreated HIV compromises the host's immune system, which makes it susceptible to opportunistic infections and malignancies, and is associated with comorbidities that affect all organ systems. When untreated, HIV advances through three stages of infection: acute infection, clinical latency, and AIDS. The development of specific comorbidities and adverse events among those with HIV is dependent on a number of factors including stage of infection, the presence of coinfections, and treatment status. Therefore providing frequency estimates of adverse events among the undiagnosed and untreated HIV population, which are also likely to differ substantially by geography, is difficult. {Bradley 2014},{Hamers 2008}. Although no effective cure currently exists, ART administered at an early stage can improve an HIV patient's prognosis, decreasing morbidity, mortality, and the risk of spreading the infection {Schwarcz 2013}. However, as the number of HIV patients with lifelong access to treatment is increasing, HIV-associated complications and chronic diseases related to inflammation, immunodeficiency, and ageing are also emerging {Deeks 2013a, Langebeek 2017}.

SI.1.5.1. Mortality and Morbidity

Access to effective treatment varies by region, and contributes to observed differences in rates of mortality. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of scaled up ART and the steady decline in HIV incidence since the peak in 1997. Since its peak in 2004, AIDS-related deaths have reduced by more than 65% {UNAIDS AidsInfo 2022a}. In 2021, this decline continued, with evidence that the drop in the number of people dying from AIDS-related causes is accelerating in several countries. In 2021, 650,000 (95% CI: 510,000-860,000) people died from AIDS-related causes worldwide {UNAIDS AidsInfo 2022a}. The leading causes of mortality and morbidity among people living with advanced HIV disease are tuberculosis and cryptococcal meningitis {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2022}, {UNAIDS 2021}.

The number of people dying from AIDS-related causes in Eastern and Southern Africa declined by 58% from 2010 to 2021, although the region still accounted for approximately 45% of all the people dying from AIDS in 2021. The percent change in AIDS-related deaths between 2010 and 2021 also decreased in Asia and Pacific (54%), Western and Central Africa (50%), Caribbean (50%), Western and Central Europe and North America (34%), Latin America (28%), and Middle East and North Africa (22%). Eastern Europe and Central Asia, however, experienced a 32% increase in mortality from AIDS during the same time {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2022}, {UNAIDS 2021}.

Following the introduction of HAART, mortality rates overall among people living with HIV declined due to decreases in both non-AIDS and AIDS-related deaths. However, the proportion of deaths associated with non-AIDS related diseases has increased in patients on ART {Ingle 2014} {Palella 2013}, {Weber 2013}.

SI.1.6. Important Co-morbidities and Co-infections

Prior to the success of ART for the treatment of HIV/AIDS, the most common co-morbidities were those traditionally defined as AIDS-related illnesses and correlated with CD4 cell count, such as Guillain-Barre Syndrome, Kaposi's sarcoma, and Non-Hodgkin's lymphoma {Hanson 1995}. As HIV patients on ART are living longer with viral suppression, the more prevalent co-morbidities are chronic health conditions in both resource-limited settings and wealthy regions {Balderson 2013, Deeks 2013b, Hirschhorn 2012, Hsue 2016}. Below is a list of important conditions that have evidence of higher risk among HIV patients and/or those accessing ART:

- Arthritis
- Bone disease (i.e, osteopenia, osteoporosis, and fracture)
- Cardiovascular disease (i.e, hypertension and hyperlipidemia)
- Chronic pain
- Endocrine disease, including diabetes

- Frailty
- Hepatitis
- Mental illness (i.e, depression and suicidal ideation)
- Neurocognitive disorders
- Other sexually transmitted diseases
- Pulmonary disease (i.e, Chronic obstructive pulmonary disease)
- Renal disease
- Some non-HIV-related malignancies (i.e, liver, cervical, anal, and Hodgkin’s lymphoma)
- Tuberculosis

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

SII.1. Eviplera

No nonclinical studies of Eviplera (EPA) have been conducted. Information on relevant safety findings for the components of EPA are presented in the tables within this section. No additional nonclinical studies are presently planned for EPA.

SII.2. Emtricitabine

Table SII.1. Table of Key Safety Findings from Non-Clinical Studies (Emtricitabine)

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Nonclinical data on FTC reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.	No safety concerns for humans are anticipated based on the non-clinical data for FTC

SII.3. Rilpivirine

Table SII.2. Table of Key Safety Findings from Non-Clinical Studies (Rilpivirine)

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
<u>Hepatotoxicity</u> Hepatocellular hypertrophy in mice and rats was associated with liver enzyme (i.e. uridine diphospho-glucuronosyltransferase [UDP GT]) induction and an increase of the organ weight. Mild to moderate perivascular inflammatory reactions together with fibrosis and single hepatic cell necrosis in the central part of the lobules were seen in dogs and were associated with an increase in cholesterol, bilirubin, alkaline phosphatase (ALP) and alanine aminotransferase (ALT). Mononuclear phagocytic system aggregates were noted and multifocal bile duct proliferation.	Careful clinical monitoring of liver function parameters was performed in clinical trials. Hepatotoxicity is not considered to be an important risk for EPA given the clinical trial data for RPV-containing regimens and postmarketing data for EPA and emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey; ODE).
<u>Thyroid and pituitary glands</u> The thyroid gland effects in rats were characterized by an increased organ weight, hypertrophy of follicular epithelium, and reduced serum concentrations of thyroxine and were associated with liver enzyme (i.e. UDP GT) induction. Effects on the pituitary gland in rats comprised an increase of swollen and vacuolated cells in the pars distalis. These effects are considered secondary to the thyroid gland effects.	As the effects on thyroid and pituitary glands are secondary to the effects of RPV on rodent specific thyroxine clearance, they are not considered relevant for humans.

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Nephrotoxicity Minimal to moderate degenerative nephropathy was noted in mice. Moderate acute nephritis was observed in dogs.	The kidney effects seen in mice and dogs are not indicative of an effect on glomerular filtration or proximal tubular resorption. For these reasons and in view of the safety margins, the nonclinical kidney effects are considered not relevant for humans.
Cardiovascular (including potential for QT interval prolongation) Rilpivirine demonstrated the potential to inhibit some potassium channels involved in cardiac action potential repolarization and to induce QT interval prolongation in the rabbit ventricular wedge assay. However, the observed mild QT interval prolongation contributed to only a marginal Torsade de Pointes (TdP) score at unbound drug concentrations much higher than those achieved in humans with the approved 25 mg dose, indicating a low proarrhythmic risk of RPV. In the in vivo animal models, no significant effect on electrophysiological cardiovascular or hemodynamic parameters was noted.	Potential for QT interval prolongation in humans, as confirmed by the dose dependent QT prolongation in the thorough QT trial (TQT) with supratherapeutic doses. However, no QT prolongation was observed with the approved 25mg dose.
Adrenal glands Changes in the serum concentrations of adrenal hormones or their precursors and of adrenocorticotropic hormone (ACTH) in rats, dogs, monkeys and likely the effects in dog testes and ovaries of mice and dogs are due to the apparent inhibition of cytochrome P450 (CYP) 21 and CYP17, key enzymes in steroidogenesis.	Potential for changes in adrenal hormones and gonadal effects in humans and eventually for adrenal insufficiency. Careful clinical monitoring of adrenal function was performed in clinical trials. Not considered a significant or relevant finding to humans given the results from monitoring in clinical trials.
Red blood cells Small decrease in red blood cell parameters was seen in mice, rats, and dogs at high doses. Signs of regeneration were noted and no signs pointed toward bone marrow suppression.	No relevance for humans given the absence of bone marrow suppression.
Coagulation system A mild to moderate increase of coagulation times of both the intrinsic and extrinsic pathways occurred only in male rats. There were no clinical manifestations of affected coagulation in this species.	Given the absence of clinical manifestations, this effect in rats only is not considered relevant for humans.
Carcinogenicity Hepatocellular adenomas and carcinomas seen in mice were associated with induction of CYP4A and peroxisome proliferation. Hepatocellular adenomas and follicular adenomas and carcinomas in thyroid gland in rats occurred as a result of induction of CYP3A and UDP-GT.	As the liver enzyme inductions underlying the carcinogenetic effects in rodents do not occur in humans, the neoplastic effects are not considered relevant for humans.
Reproductive and Developmental toxicity The reproductive and developmental toxicity studies did not demonstrate any effects on the development of offspring from dams treated with RPV during pregnancy and lactation. Rilpivirine did not show a teratogenic potential or effect on reproductive function. The reproductive and developmental toxicity studies did not demonstrate any effects on fertility or fecundity, parturition, or maternal behavior.	No safety concerns have been identified for humans based on nonclinical studies of reproductive and developmental toxicity.

SII.4. Tenofovir DF

Table SII.3. Table of Key Safety Findings from NonClinical Studies (Tenofovir DF)

Key Safety Findings from Non-clinical studies	Relevance to Human Usage
Nonclinical safety pharmacology studies reveal no special hazard for humans (D990155, R990152, R990153, R990154). Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Evidence of renal toxicity was noted in four animal species exposed to TFV and TDF in nonclinical studies. Increases in serum creatinine, blood urea nitrogen (BUN), glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. In rats and mice, renal tubular karyomegaly was observed. In dogs and monkeys renal tubular degeneration/regeneration was observed in addition to karyomegaly. The incidence, severity and reversibility of the histopathological changes were related to dose and duration of treatment. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans after a 300 mg daily dose. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in pediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.	*Renal toxicity is an important identified risk for TDF.* Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal renal tubulopathy (PRT) (including Fanconi syndrome) have been reported with the use of TDF (EPA SmPC). *Bone events due to PRT / loss of BMD is an important identified risk for TDF.* Decreases in BMD observed following the initiation of antiretroviral therapy (ART) appear to be greater with regimens containing TDF compared to those without TDF. Osteomalacia (infrequently contributing to fractures) may be associated with PRT (EPA SmPC).
Genotoxicity studies revealed positive results in the *in vitro* mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an unscheduled DNA synthesis (UDS) test in primary rat hepatocytes. However, it was negative in an *in vivo* mouse bone marrow micronucleus assay. Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumors at an extremely high dose in mice.	These tumors are unlikely to be of relevance to humans.
Reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or fetal parameters. Tenofovir DF reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.	No safety concerns for humans are anticipated based on the non-clinical reproductive studies for TDF.

SII.5. Conclusions on Nonclinical Data

Table SII.4. Safety Concerns from Nonclinical Data

	Safety Concern
Important Identified Risks (confirmed by clinical data)	Renal toxicity (TDF)
	Bone events due to proximal renal tubulopathy/loss of bone mineral density (TDF)
Important Potential Risks (not refuted by clinical data or which are of unknown significance)	None
Missing information	None

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

The marketing authorization for EPA approved on 28 November 2011 was based on the results of the Phase 3 clinical studies of RPV in combination with FTC/TDF in antiretroviral treatment (ART) naïve adult patients (Studies TMC278-C209 and TMC278-C215). The single-tablet regimen (STR), EPA, was subsequently studied in ART naïve patients (Study GS-US-264-0110), and virologically suppressed patients who switched from a regimen containing a ritonavir-boosted protease inhibitor (PI/r) and 2 NTRIs (Study GS-US-264-0106) or from efavirenz/FTC/TDF (Phase 2b study GS-US-264-0111).

The tables in this section present clinical trial exposure data to Eviplera (as a STR) cumulative to 11 April 2019 in subjects with HIV-1 infection from the following completed Gilead-sponsored clinical studies:

- GS-US-264-0106, GS-US-264-0110, GS-US-264-0111, and GS-US-366-1216

Table SIII.1. Duration of Exposure in Subjects with HIV-1 Infection

Duration Of Exposure	Patients	Person-years
≥ 1 day	1226	1856
> 30 days	1216	1855
> 90 days	1188	1850
> 180 days	1067	1797
> 1 year	771	1535
> 2 years	323	759
> 3 years	14	45

Table SIII.2. Exposure by Age Group and Gender in Subjects with HIV-1 Infection

	Patients		Person-years	
Age Group	Male	Female	Male	Female
< 18 years	0	0	0	0
18-30 years	210	21	321	31
31-40 years	322	27	483	34
41-50 years	381	42	580	54
51-65 years	185	26	299	36
66-75 years	12	0	20	0
> 75 years	0	0	0	0

Table SIII.3. Exposure by Ethnic origin in Subjects with HIV-1 Infection

Ethnic origin	Patients	Person-years
American Indian or Alaska Native	10	13
Asian	36	61
Black or African American	239	344
Native Hawaiian or Pacific Islander	5	9
White	901	1380
Other	33	47
Missing	1	2
Not permitted	1	2

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Medicinal products excluded from concurrent use: anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin); antimycobacterials, (rifampicin, rifapentine); proton pump inhibitors, (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole); systemic glucocorticoid (dexamethasone [more than a single dose]); and St John's wort (Hypericum perforatum).	The exposure to these medicinal products may lead to significant decreases in RPV plasma concentrations (due to CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of EPA.	No Rationale:Coadministration is contraindicated in the EPA SmPC.
Pregnant females and females who are breastfeeding	Limited information on the use in this patient population.	Safety in lactation: No Safety in pregnancy: No Rationale: Based on the Antiretroviral Pregnancy Registry report (data to 31July2024), for individual components of Eviplera sufficient numbers of first trimester exposures (Emtricitabine [n=5250], Rilpivirine [n=770], TDF [N=5076]) have been monitored with no increase in birth defects detected. The Eviplera SmPC contains guidance on use during pregnancy and lactation.
Subjects with renal impairment (calculated creatinine clearance [Cl_{cr}] < 50 or < 70 mL/min)	Limited information on the use in this patient population.	Yes Safety in patients with renal impairment is considered missing information for TDF.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Table SIV.2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are uncommon	1226 HIV-1 infected subjects have been exposed to EPA in clinical studies	The clinical trial population is large enough to detect at least some uncommon adverse drug reactions (ADRs). ADRs with a frequency greater than 1 in 409 could potentially be detected if there was no background incidence.
Due to prolonged exposure	323 HIV-1 infected subjects have been exposed to EPA for more than 2 years and 14 HIV-1 infected subjects have been exposed to EPA for more than 3 years in clinical studies.	No ADRs specifically associated with prolonged exposure to EPA have been identified in the EPA clinical trial program.
Due to cumulative effects	323 HIV-1 infected subjects have been exposed to EPA for more than 2 years and 14 HIV-1 infected subjects have been exposed to EPA for more than 3 years in clinical studies.	No cumulative effects to EPA have been identified in the EPA clinical trial program.
Which have a long latency	323 HIV-1 infected subjects have been exposed to EPA for more than 2 years and 14 HIV-1 infected subjects have been exposed to EPA for more than 3 years in clinical studies.	No ADRs to EPA with a long latency have been identified in the EPA clinical trial program.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table SIV.3. Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of special population	Exposure	Considered to be Missing Information
Pregnant and breastfeeding women	Pregnant and breastfeeding women were excluded from enrolling in clinical studies. Five pregnancy cases were reported in patients receiving EPA in the EPA clinical development program. No cases involving breastfeeding women were reported in the GS-sponsored EPA clinical trials.	Safety in lactation: No Safety in pregnancy: No Rationale: Based on the Antiretroviral Pregnancy Registry report (data to 31July2024), for individual components of Eviplera sufficient numbers of first trimester exposures (Emtricitabine [n=5250], Rilpivirine [n=770], TDF [N=5076]) have been monitored with no increase in birth defects detected. The Eviplera SmPC contains guidance on use during pregnancy and lactation.
Children (including long-term safety)	Subjects < 18 years were excluded from enrolling in clinical studies.	No Rationale: EPA is not indicated for the treatment of patients < 18 years old (EPA SmPC)
Elderly	As of 10 August 2018, 12 subjects (20 person-years) over 65 years old were exposed to EPA in the GS-sponsored EPA clinical trials.	No Rationale: Case reports involving elderly patients have been monitored through routine PV activities, including periodic safety update reports (PSURs), since marketing approval of EPA, no safety concern has been identified.
Patients with moderate to severe renal impairment	Not included in Pivotal Phase 3 studies	No Rationale: Safety data for patients with renal impairment has been monitored through routine PV activities, including PSURs, and no safety concern has been identified.
Patients with severe hepatic impairment (CPT score C)	Not known. Patients had to have hepatic transaminases (AST and ALT) ≤ 5 × upper limit of normal (ULN) and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin to be enrolled.	No Rationale: No new safety concerns for EPA are anticipated. Since the marketing of EPA, no AE cases involving use of EPA in patients with severe hepatic impairment have been reported. The PK of FTC have not been studied in subjects with hepatic impairment, however, as FTC is not significantly metabolized by liver enzymes the impact of hepatic impairment should be limited. RPV has not been studied in patients with severe hepatic impairment. RPV has not been studied in patients with severe hepatic impairment. The PK of tenofovir after a 300 mg dose of TDF are not substantially altered in patients with hepatic impairment compared with unimpaired patients (study GS-01-931).

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1. Post-Authorization Exposure

SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed Eviplera/Complera has been estimated from both sales data and from prescription data and is reported in applicable periodic safety update reports/periodic benefit-risk evaluation reports (PSURs/PBRERs). The methodology used to calculate patient exposure from these two sources is described below:

Sales data

The number of bottles sold cumulatively was multiplied by 30 to provide the number of tablets sold. As Eviplera/Complera is taken as a once-daily dose, the total numbers of tablets were divided by 365.25 to provide patient-years of treatment. It should be noted that the use of sales data for patient exposure calculations will tend to overestimate exposure, due to the accumulation of drug stocks at pharmacies/distributors. This method of estimating exposure to marketed product is felt to be justified since the overwhelming majority of patients receiving Eviplera/Complera will be adults receiving the standard daily dose over a relatively long period of time.

Prescription data

- Estimates of the demographics data of HIV infected patients exposed to Eviplera/Complera in the 5 major European countries: United Kingdom, France, Germany, Italy and Spain were obtained from the following sources:

  — IQVIA/Groupement pour l'Élaboration et la Réalisation de Statistiques (GERS): IQVIA data in the EU provides details of the number of bottles prescribed (no details are provided on whether a prescription is a repeat or an initial prescription). The data is obtained through a comprehensive panel of pharmacies and wholesalers. GERS data is based on a syndicate of manufacturers and wholesalers who provide their transactions and is available in France only; GERS data is combined with IQVIA data.

  — *Ipsos Monitor:* The Ipsos Healthcare HIV EU Therapy Monitor study is a syndicated, bi-annual diary study involving HIV treating physicians and data has been obtained from April 2022 to June 2022. A total of 200 HIV treating physicians are involved across the 5 main European countries and the sample is regionally representative of the prevalence of HIV infection in each country. The physicians are screened to ensure they see at least 15 HIV patients per week and manage the care of at least 50 HIV patients. Each physician completes patient record forms for the next 8 patients they see during the fieldwork period. All patients are currently receiving ARV therapy and these patients could be initiating, switching, or maintaining antiretroviral therapy (ART). In the 5 main European countries (Q2'22), this dataset consists of 1569 patient records.

SV.1.2. Post-Authorization Exposure

SV.1.3. Exposure based on Sales Data

Based on sales data, the cumulative global patient exposure to Eviplera since first marketing approval on 10 August 2011 to 10 August 2023 is estimated to be 814,588 patient-years of treatment. Further information on cumulative patient exposure by geographic areas is provided in the PSUR/PBRER for Eviplera.

SV.1.4. Exposure based on Prescription Data

Based on prescription data from the UK, France, Germany, Italy, and Spain, most patients exposed to Eviplera were male and the majority of patients (49%) were aged 40-59 years.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for Eviplera to be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an updated RMP

No new important identified risks, important potential risks or missing information have been identified or reclassified for Eviplera since the submission of the last RMP.

Risks previously classified as important, and missing information, removed from the list of safety concerns, along with the reasons for their removal, are presented in Table SIV.1.

Table SIV.1. Reason for Removing an Important Identified or Potential Risk or Missing Information from the List of Safety Concerns in the RMP

Safety Concern Removed	Reason for Removal from the List of Safety Concerns
Identified Risks	
Renal toxicity (TDF)	Risk is to be removed from the list of safety concerns and will continue to be monitored by routine PV activities. There are no outstanding additional risk minimization measures or additional PV activities for this risk. Renal messages are included in the European treatment guidelines for HIV infection {European AIDS Clinical Society (EACS) 2020} {Bamford 2015} and the renal monitoring recommendations are provided in the EU SmPC for Eviplera. Given that renal toxicity risk minimization measures in both adolescents and adults have become fully integrated into standard clinical practice (through inclusion in treatment guidelines), the risk is considered fully characterized and appropriately managed. Renal toxicity will continue to be monitored through routine pharmacovigilance and any significant new safety information for renal toxicity will be summarized and presented in relevant sections of future PSUR/PBRERs as requested by PRAC under procedure EMA/VR/0000287296.
Bone events due to proximal renal tubulopathy/loss of BMD	Risk is to be removed from the list of safety concerns and will continue to be monitored by routine PV activities. There are no outstanding additional risk minimization measures or additional PV activities for this risk. Warnings in regard to bone events are included in the EU SmPC for Eviplera and bone effects and screening recommendations are included in the European treatment guidelines for HIV infection {European AIDS Clinical Society (EACS) 2020} {Bamford 2015}. Given that the management of this risk is fully integrated into standard clinical practice (through inclusion in treatment guidelines), this risk is considered fully characterized and appropriately managed.

Safety Concern Removed	Reason for Removal from the List of Safety Concerns
	This risk will continue to be monitored through routine pharmacovigilance and any new significant safety information for bone events due to proximal renal tubulopathy/loss of BMD will be summarized and presented in relevant sections of future PSUR/PBRERs as requested by PRAC under procedure EMA/VR/0000287296.
Missing information	
Safety in patients with renal impairment	Safety data for patients with renal impairment has been monitored through routine PV activities, including PSURs, and no safety concern has been identified. There are no outstanding pharmacovigilance activities.
Safety in pregnancy and lactation	Based on the Antiretroviral Pregnancy Registry report (data to 31July2024), for individual components of Eviplera sufficient numbers of first trimester exposures (Emtricitabine [n=5250], Rilpivirine [n=770], TDF [N=5076]) have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems. No such increases have been detected to date. No further information on pregnancy is needed to further characterize this risk. According to the Eviplera EU SmPC, between 300-1,000 pregnancy outcomes associated with rilpivirine and more than 1,000 pregnancy outcomes associated with emtricitabine and TDF indicate no malformations or foetal/neonatal toxicity. There is adequate information in Section 4.6 of Eviplera EU SmPC for the healthcare professional to make an informed decision regarding use of Eviplera in pregnancy and to advise the patient appropriately. Additionally, management of this risk is fully integrated into standard clinical practice through inclusion in treatment guidelines {European Aids Clinical Society (EACS) 2025}. According to the Eviplera EU SmPC, emtricitabine and tenofovir disoproxil are excreted in human milk. It is not known whether rilpivirine is excreted in human milk. Rilpivirine is excreted in the milk of rats. There is insufficient information on the effects of Eviplera in newborns/infants. Because of the potential for adverse reactions in breastfed infants, women should be instructed not to breast-feed if they are receiving Eviplera. There is adequate information in Section 4.6 of the Eviplera EU SmPC for the healthcare professional to make an informed decision regarding use of Eviplera during lactation, and to advise the patient appropriately. Additionally, management of this risk is fully integrated into standard clinical practice through inclusion in treatment guidelines {European Aids Clinical Society (EACS) 2025}. No additional information on lactation is needed to further characterize this missing information and has been recommended for removal by PRAC under procedure EMA/VR/0000287296.

Following removal of these safety concerns by the MAH, there will be no safety concerns for Eviplera in the EU-RMP.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

There are no important identified risks for Eviplera or its components.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for Eviplera or its components.

SVII.3.2. Presentation of the Missing Information

There is no missing information for Eviplera or its components.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

There are no adverse reaction follow-up questionnaires for Eviplera.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study title	Rationale and Study Objectives	Study Design and Study Populations	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV:
PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

IV.1. PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing post-authorization efficacy studies for EPA.

PART V:
RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1. ROUTINE RISK MINIMIZATION MEASURES

The routine risk minimization measure for Eviplera in the EU comprise of the SmPC, the package leaflet (PL), and the legal status of the product. Eviplera is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV (SmPC section 4.2).

The routine risk minimization recommendations provided by the SmPC and PL are described further by safety concern in Table Part V 1. The legal status can be considered a general measure and not associated with a safety concern.

Table Part V 1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
None	
Important Potential Risks	
None	
Missing Information	
None	

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. SUMMARY RISK MINIMIZATION MEASURES

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None		
Important potential risk(s)		
None		
Missing information		
None		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. SUMMARY OF RISK MANAGEMENT PLAN FOR EVIPLERA (EMTRICITABINE/RILPIVIRINE/TENOFOVIR DISOPROXIL FUMARATE)

This is a summary of the risk management plan (RMP) for Eviplera. The RMP details important risks of Eviplera, how these risks can be minimized, and how more information will be obtained about Eviplera's risks and uncertainties (missing information).

Eviplera's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Eviplera should be used.
This summary of the RMP for Eviplera should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Eviplera's RMP.

II. The Medicine and What is it Used for

Eviplera is authorized for treatment of adults infected with HIV 1 without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine and with a viral load ≤ 100,000 HIV 1 RNA copies/mL (see SmPC for the full indication). It contains emtricitabine (FTC), rilpivirine (RPV) and tenofovir disoproxil fumarate (TDF) as the active substance and it is given orally.

Further information about the evaluation of Eviplera's benefits can be found in Eviplera's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/eviplera

III. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Eviplera, together with measures to minimize such risks and the proposed studies for learning more about Eviplera's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimizes its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Eviplera is not yet available, it is listed under 'missing information' below.

III.A. List of important risks and missing information

Important risks of Eviplera are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Eviplera. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

III.B. Summary of Important Risks

There are no important identified, potential risks or missing information for Eviplera. Eviplera has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy should be initiated by a doctor experienced in the management of HIV infection (as described in section 4.2 of the SmPC).

III.C. Post-authorization Development Plan

III.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Eviplera.

III.C.2. Other Studies in Post-Authorization Development Plan

There are no studies within the post-authorization development plan.

PART VII: ANNEXES

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

None

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

- Referenced material (Refer to References)

Annex 8. Summary of Changes to the Risk Management Plan over Time

1. REFERENCES

Balderson BH, Grothaus L, Harrison RG, McCoy K, Mahoney C, Catz S. Chronic Illness Burden and Quality of Life in an Aging HIV Population. AIDS Care 2013;25 (4):451-8.

Bamford A, Turkova A, Lyall H, Foster C, Klein N, Bastiaans D, et al. Paediatric European Network for Treatment of AIDS (PENTA) guidelines for treatment of paediatric HIV-1 infection 2015: optimizing health in preparation for adult life. HIV Med 2015.

Bradley H, Hall HI, Wolitski RJ, Van Handel MM, Stone AE, LaFlam M, et al. Vital Signs: HIV diagnosis, care, and treatment among persons living with HIV--United States, 2011. MMWR Morb Mortal Wkly Rep 2014;63 (47):1113-7.

Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet 2013a;382 (9903):1525-33.

Deeks SG, Tracy R, Douek DC. Systemic Effects of Inflammation on Health During Chronic HIV Infection. Immunity 2013b;39 (4):633-45.

European AIDS Clinical Society (EACS). Guidelines Version 10.1 (English). October. 2020:

European Aids Clinical Society (EACS). EACS Guidelines, Version 11.0 (October 2021). 2021:

European Aids Clinical Society (EACS). Pregnancy and HIV. Available at: https://eacs.sanfordguide.com/eacs-part1/art/eacs-pregnancy-and-hiv. Accessed on: 27 May. 2025:

Hamers FF, Phillips AN. Diagnosed and undiagnosed HIV-infected populations in Europe. HIV Med 2008;9 (Suppl 2):6-12.

Hanson DL, Chu SY, Farizo KM, Ward JW. Distribution of CD4+ T lymphocytes at diagnosis of acquired immunodeficiency syndrome-defining and other human immunodeficiency virus-related illnesses. The Adult and Adolescent Spectrum of HIV Disease Project Group. Arch Intern Med 1995;155 (14):1537-42.

Hirschhorn LR, Kaaya SF, Garrity PS, Chopyak E, Fawzi MC. Cancer and the 'Other' Noncommunicable Chronic Diseases in Older People Living with HIV/AIDS in Resource-Limited Settings: A Challenge to Success. AIDS 2012;26 (Suppl. 1):S65-75.

HIV Infections. Combination prevention People receiving pre-exposure prophylaxis PrEP National. 2022a:

HIV infections. Epidemic trainsition metrics Trend of new HIV infections regional. 2022b:

HIV Infections. People living with HIV Number of people living with HIV Population Adults 15 FEMALE regional. 2022c:

Hsue P, Shreay S, Song X, Meyer N. A Longitudinal Analysis of Comorbidities among Human Immunodeficiency Virus (HIV) Patients and Matched non-HIV Controls in the USA [Abstract 950]. ID Week™; 2016 26-30 October; New Orleans, LA.

infections NH. HIV incidence per 1000 population all ages regional. 2022a:

infections NH. HIV incidence per 1000 population young women 15 - 24 regional. 2022b:

infections NH. New HIV infections 15 - 24 FEMALES regional. . 2022c:

infections NH. New HIV infections all ages FEMALES regional. 2022d:

infections NH. New HIV infections all ages MALES regional. 2022e:

infections NH. New HIV infections all ages regional. 2022f:

Ingle SM, May MT, Gill MJ, Mugavero MJ, Lewden C, Abgrall S, et al. Impact of risk factors for specific causes of death in the first and subsequent years of antiretroviral therapy among HIV-infected patients. Clin Infect Dis 2014;59 (2):287-97.

Joint United Nations Programme on HIV/AIDS (UNAIDS). Children and HIV: Fact Sheet. Available at: http://www.unaids.org/en/resources/documents/2014/20140508_FactSheet_Children. 12 July. 2016.

Joint United Nations Programme on HIV/AIDS (UNAIDS). A Special Supplement to the UNAIDS Report on the Global AIDS Epidemic 2013: HIV and Aging. Accessed 09 June. Geneva, Switzerland. 2017.

Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data. Geneva, Switzerland. 2020.

Joint United Nations Programme on HIV/AIDS (UNAIDS). IN DANGER: UNAIDS Global AIDS Update 2022. 2022.

Langebeek N, Kooij KW, Wit FW, Stolte IG, Sprangers MAG, Reiss P, et al. Impact of Comorbidity and Ageing on Health-Related Quality of Life in HIV-Positive and HIV-Negative Individuals. AIDS 2017;31 (10):1471-81.

Mahy M, Autenrieth CS, Stanecki K, Wynd S. Increasing Trends in HIV Prevalence Among People Aged 50 Years and Older: Evidence from Estimates and Survey Data. AIDS 2014;28 (Suppl. 4):S453-9.

Nakagawa F, May M, Phillips A. Life Expectancy Living with HIV: Recent Estimates and Future Implications. Curr Opin Infect Dis 2013;26 (1):17-25.

New HIV infections. Number of new infections Population Adults (15+). 2022a:

New HIV infections. Number of new infections Population Children 0 14 regional. 2022b:

Palella FJ, Buchacz K, Debes R, Baker R, Armon C, Brooks JT, et al. Continued Declines In Mortality Are Largely Due To Reductions In Non-Aids Related Deaths, And Mortality Remains Disproportionately Higher Among Blacks And The Publicly Insured In The Hiv Outpatient Study (Hops), 1996–2009 [PIN25]. Value in Health 2013;16 (3):A83.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines . Revised Date: January 2022. 2022:

Schwarcz L, Chen MJ, Vittinghoff E, Hsu L, Schwarcz S. Declining incidence of AIDS-defining opportunistic illnesses: results from 16 years of population-based AIDS surveillance. AIDS 2013;27 (4):597-605.

Teeraananchai S, Kerr SJ, Amin J, Ruxrungtham K, Law MG. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. HIV Med 2017;18 (4):256-66.

UNAIDS. 2013 Global Fact Sheet. 2013.

UNAIDS. Fact Sheet - Global HIV Statistics 2021. 2021:

UNAIDS AidsInfo. New HIV infections - Number of new infections - Population - Children (0-14) - regional. Available at: https://aidsinfo.unaids.org/. Accessed: 03 August. 2021:

UNAIDS AidsInfo. AIDS-related deaths-Number of AIDS-related deaths-Population-All ages-regional. Available at: https://aidsinfo.unaids.org/. Accessed: 07 October. 2022a:

UNAIDS AidsInfo. Full Report - In Danger: UNIAIDS Global AIDS Update. Available at: https://aidsinfo.unaids.org/. Accessed: 24 November 2022. Last Updated: 27 July. 2022b:

UNAIDS AidsInfo. People living with HIV-HIV Prevalence-Population-Adults (15+)-regional. Available at: https://aidsinfo.unaids.org/. Accessed: 07 October. 2022c:

UNAIDS AidsInfo. People living with HIV-Number of people living with HIV-Population-Adults (15+)-regional. Available at: https://aidsinfo.unaids.org/. Accessed: 07 October. 2022d:

UNAIDS AidsInfo. People living with HIV-Number of people living with HIV-Population-All ages-regional. Available at: https://aidsinfo.unaids.org/. Accessed: 07 October. 2022e:

UNAIDS AidsInfo. People living with HIV-Number of people living with HIV-Population-Children (0-14)-regional. Available at: https://aidsinfo.unaids.org/. Accessed: 07 October. 2022f:

Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. Curr Opin HIV AIDS 2016;11 (5):492-500.

Weber R, Ruppik M, Rickenbach M, Spoerri A, Furrer H, Battegay M, et al. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. HIV Med 2013;14 (4):195-207.

Wing EJ. HIV and Aging. Int J Infect Dis 2016;53:61-8.

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

There are no specific adverse drug reaction follow-up forms for Eviplera.