EU Risk Management Plan for Viread® (Tenofovir Disoproxil Fumarate)

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RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
27.0	08 May 2025	28 Oct 2025

Rationale for submitting an updated RMP:

This RMP was updated to remove:

- Important identified risks of:
  - Renal toxicity
  - Bone events due to proximal renal tubulopathy/loss of bone mineral density (BMD)
- Additional pharmacovigilance activities of:
  - Monitoring of reversibility of renal tubulopathy in clinical trials
- Missing information of:
  - Safety in patients with renal impairment
  - Safety in pregnancy and lactation
- Targeted questionnaires related to bone and renal risks corresponding to important identified risks and missing information

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part I Product Overview	Indication(s) in the EEA	None.
	Dosage in the EEA	None
Part II Safety Specification	Part II: Module SI: Epidemiology of the indication and target populations(s)	Updated to reflect removal of the important identified risks "Renal toxicity" and "bone events due to proximal renal tubulopathy/loss of BMD" and rationale for removal of these important identified risks. Further updated to remove "Safety in patients with renal impairment" and "Safety in pregnancy and lactation"
	Part II: Module SII: Non-clinical part of the safety specification	
	Part II: Module SIII: Clinical trial exposure	
	Part II: Module SIV: Populations not studied in clinical trials	

Part	Module/Annex	Significant changes to RMP
	Part II: Module SV: Post-authorization experience	from missing information with rationale for removal.
	Part II: Module SVI: Additional EU requirements for the safety specification	
	Part II: Module SVII: Identified and potential risks	
	Part II: Module SVIII: Summary of the safety concerns	
Part III Pharmacovigilance Plan		Removal of targeted questionnaires collecting information on bone and renal events. Removal of "Monitoring of reversibility of renal tubulopathy in clinical trials" and the Antiretroviral Pregnancy Registry (APR) from additional pharmacovigilance activities.
Part IV Plan for post-authorization efficacy studies		None.
Part V Risk Minimization Measures		Updated to reflect the removal of the important identified risks "renal toxicity" and "bone events due to proximal renal tubulopathy/loss of BMD". Updated to remove "safety in patients with renal impairment" and "safety in pregnancy and lactation" from missing information, and the consequent removal of the antiretroviral pregnancy registry as an additional pharmacovigilance activity.
Part VI Summary of RMP		Updated to reflect the removal of the important identified risks "renal toxicity" and "bone events due to proximal renal tubulopathy/loss of BMD" and the pharmacovigilance activity "monitoring of reversibility of renal tubulopathy in clinical trials". Updated to remove "safety in patients with renal impairment" and "safety in pregnancy and lactation" from missing information, and the consequent removal of the antiretroviral pregnancy registry as an additional pharmacovigilance activity.

Part	Module/Annex	Significant changes to RMP
Part VII Annexes		Annexes 2, 3, 4 and 8 were updated to reflect the removal of the targeted questionnaires on bone and renal events, the removal of the pharmacovigilance activity "monitoring of reversibility of renal tubulopathy in clinical trials" and Antiretroviral Pregnancy Registry (APR) as well as the removal of safety concerns, as applicable.

Other RMP versions under evaluation:

None.

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
26	EMEA/H/C/000419/II/0204	24 February 2022

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
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	antiretroviral
AUC	area under the curve
BMD	bone mineral density
CCDS	company core data sheet
CDC	Centers for Disease Control and Prevention
CD4	antigenic marker on helper/inducer T cells
CHB	chronic hepatitis B
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
CL_{cr}	creatinine clearance
CPT	Child-Pugh-Turcotte classification
CSR	clinical study report
dATP	deoxyadenosine triphosphate
ddI	didanosine
DEXA	dual-energy x-ray absorptiometry
DHHS	Department of Health and Human Services
DLP	data lock point
DNA	deoxyribonucleic acid
DRV	darunavir
EACS	European AIDS Clinical Society
EAP	expanded access programme
EASL	European Association for the Study of the Liver
ECDC	European Center for Disease Prevention and Control
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU-RMP	European Union Risk Management Plan
FTC	emtricitabine
GERS	Groupement pour l'Élaboration et la Réalisation de Statistiques
GFR	glomerular filtration rate
GN	glomerulonephritis

GVP	Good Pharmacovigilance Practices
HAART	highly active antiretroviral therapy
HBeAg	hepatitis B early antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCP	healthcare professional
HCV	hepatitis C virus
HIV (-1)	human immunodeficiency virus (type 1)
hOAT	human organic anion transporter
IDU	injection drug users
INSTI	integrase strand transfer inhibitor
MAH	Marketing Authorization Holder
MITOC Group	European collaboration on mitochondrial toxicity in children and NRTI exposure during pregnancy
MRP	multi-drug resistance protein
MSM	men who have sex with men
NA	nucleos(t)ide analogue
N/A	not applicable
NIH	(US) National Institutes of Health
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleos(t)ide reverse transcriptase inhibitor
NSAID(s)	non-steroidal anti-inflammatory drug(s)
NtRTI	nucleotide reverse transcriptase inhibitor
OLT	orthotopic liver transplant
PI	protease inhibitor
PK	pharmacokinetic
PL	package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PRT	proximal renal tubulopathy
PSUR	periodic safety update report
PV	pharmacovigilance
PYFU	person-years of follow-up
RMP	risk management plan
RPV	rilpivirine
SmPC	Summary of Product Characteristics
TDF	tenofovir disoproxil fumarate
UDS	unscheduled DNA synthesis
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
US	United States
WHO	World Health Organization

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Tenofovir disoproxil fumarate (TDF)
Pharmaco-therapeutic group(s) (ATC Code):	Nucleoside and nucleotide reverse transcriptase inhibitors (J05AF07)
Marketing Authorization Holder	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Viread
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: TDF, an oral prodrug of tenofovir, is a nucleotide reverse transcriptase inhibitor (NtRTI).
	Summary of mode of action: Following absorption, TDF is rapidly converted to tenofovir, which is metabolized intracellularly to the active metabolite, tenofovir diphosphate (PMPApp). 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	Viread Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Treatment of HIV-1 infected adults in combination with other antiretroviral medicinal products. Treatment of HIV-1 infected pediatric patients, with NRTI resistance or toxicities precluding the use of first line agents, from 2 years of age and above. Treatment of chronic hepatitis B in adults with: • compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis • evidence of lamivudine-resistant hepatitis B virus • decompensated liver disease Treatment of chronic hepatitis B in adolescents 2 to < 18 years of age with compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis.
	Proposed: Not applicable.

Dosage in the EEA	Current: The recommended dose of Viread for the treatment of HIV-1 infection or for the treatment of chronic hepatitis B in adults is one 245 mg tablet once daily taken orally with food. The recommended dose of Viread for the treatment of HIV-1 infection or for the treatment of chronic hepatitis B in adolescents aged 12 to < 18 years and weighing ≥ 35 kg is one 245 mg tablet once daily taken orally with food. The recommended dose for HIV-1 infection or for the treatment of chronic hepatitis B in pediatric patients aged 6 to < 12 years weighing 28 kg to < 35 kg is one 204 mg tablet once daily taken orally with food. The recommended dose for HIV-1 infection or for the treatment of chronic hepatitis B in pediatric patients aged 6 to < 12 years weighing 22 kg to < 28 kg is one 163 mg tablet once daily taken orally with food. The recommended dose for HIV-1 infection or for the treatment of chronic hepatitis B in pediatric patients aged 6 to < 12 years weighing 17 kg to < 22 kg is one 123 mg tablet once daily taken orally with food. The recommended dose for HIV-1 infection or for the treatment of chronic hepatitis B in pediatric patients aged 2 to < 6 years is 6.5 mg of tenofovir disoproxil (as fumarate) per kg of body weight once daily taken orally (as granules) with food.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Film-coated tablet/300 mg tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) Film-coated tablet/250 mg tenofovir DF (equivalent to 204 mg of tenofovir disoproxil) Film-coated tablet/200 mg tenofovir DF (equivalent to 163 mg of tenofovir disoproxil) Film-coated tablet/150 mg tenofovir DF (equivalent to 123 mg of tenofovir disoproxil) Granules for oral use 40 mg/g tenofovir DF (equivalent to 33 mg/g of tenofovir disoproxil)
	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-1 Infection

SI.1.1. Incidence

The number of people (adults and children) acquiring human immunodeficiency virus (HIV) infection in 2016 was 1.8 million [95% CI: 1.6 million-2.1 million]) (Table SI.1). Worldwide, this number continues to decrease over time. Among adults, there was an 11% decline between 2010 and 2016, with the total number of new adult infections in 2016 estimated at 1.7 million (95% CI: 1.4-1.9 million) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018c}. Among children, the number of new infections in 2016 (n=160,000 [95% CI: 100,000-220,000]) declined by 47% during the same time (2010 to 2016) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018e}. The annual number of new HIV infections among adults and adolescents decreased by 50% or more in 26 countries between 2001 and 2012. The declining rates observed in low- and middle-income countries over this time period primarily represent a reduction in sexual transmission. More recently, however, declines in incidence rates have slowed, with variations across geographic regions and disparate groups within them {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017c}. Within the geographic regions defined by UNAIDS, new HIV infections have been on the rise in Eastern Europe and Central Asia, with an increase of 58% between 2010 and 2016, due to increases from among injection drug users (IDU). Overall, incidence has remained constant in Western and Central Europe and North America {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017c}, {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017a}, {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018d}. Increases in incidence rates were observed among men who have sex with men (MSM) between 2010 and 2014 in Western and Central Europe and North America, while rates decreased among IDU in North America during the same time {Centers for Disease Control and Prevention (CDC) 2016}, {European Center for Disease Prevention and Control (ECDC) 2015}.

Table SI.1. Regional Prevalent and Incident Cases of HIV Infection in 2016.

	Prevalent Cases (n; 95% CI)		Incident Cases (n; 95% CI)	
	Overall	**Adults[a]**	**Overall**	**Adults[a]**
Asia and Pacific	5.1 million (3.9-7.2 million)	4.9 million (3.7-6.8 million)	270,000 (190,000-370,000)	250,000 (180,000-380,000)
Caribbean	310,000 (280,000-350,000)	300,000 (270,000-340,000)	18,000 (15,000-22,000)	17,000 (14,000-21,000)
Eastern and Southern Africa	19.4 million (17.8-21.1 million)	18.1 million (16.6-19.7 million)	790,000 (710,000-870,000)	710,000 (630,000-790,000)
Eastern Europe and Central Asia	1.6 million (1.4-1.7 million)	1.5 million (1.4-1.7 million)	190,000 (160,000-220,000)	190,000 (160,000-220,000)
Latin America	1.8 million (1.4-2.1 million)	1.7 million (1.4-2.1 million)	97,000 (79,000-120,000)	96,000 (78,000-120,000)
Middle East and North Africa	230,000 (160,000-380,000)	220,000 (160,000-320,000)	18,000 (11,000-39,000)	17,000 (10,000-36,000)
Western and Central Africa	6.1 million (4.9-7.6 million)	5.6 million (4.5-6.9 million)	370,000 (270,000-490,000)	310,000 (220,000-410,000)
Western and Central Europe and North America	2.1 million (2.0-2.3 million)	2.1 million (2.0-2.3 million)	73,000 (68,000-78,000)	72,000 (67,000-78,000)
Total[b]	**36.7 million (30.8-42.9 million)**	**34.5 million (28.8-40.2 million)**	**1.8 million (1.6-2.1 million)**	**1.7 million (1.4-1.9 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: {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017c}

SI.1.2. Prevalence

The distribution of HIV infected individuals varies enormously across geographical regions. Approximately 34.5 million adults and 2.1 million children were living with HIV globally at the end of 2016 (total: 36.7 million; 95% confidence interval [CI]: 30.8-42.9 million). An estimated 0.8% (95% CI: 0.7-0.9%) of adults between the ages of 15 and 49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. (Table SI.1){Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017c}.

Within the geographic regions defined by UNAIDS, the Eastern and Southern Africa region is most severely affected, with nearly 1 in every 15 adults (19.4 million [95% CI: 17.8-21.1 million]) living with HIV infection in 2016. Although this region comprises 6.2% of the global population, it accounts for over 50% of people living with HIV worldwide. Western and Central Africa is the second most affected region with 6.1 million (95% CI: 4.9-7.6 million) people living with HIV. In both these African regions, which are referred to collectively as Sub-Saharan Africa, prevalence is high among key populations including MSM, sex workers,

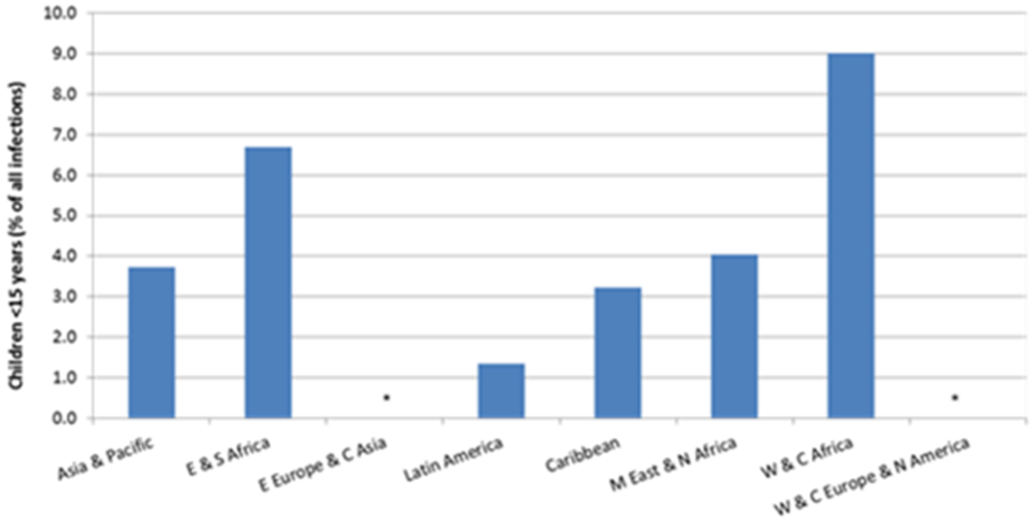
IDUs, and sexual partners of these groups. After Sub-Saharan Africa, the regions most heavily affected are Eastern Europe and Central Asia, Latin America and the Caribbean where 0.5-0.9% of adults were living with HIV in 2016. Eastern Europe and Central Asia is the only region where HIV prevalence remains on the rise. The number of people living with HIV in this region has more than tripled since 2000 and reached an estimated 1.6 million in 2016, due to a surge of infections among IDU and their sexual partners {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017c}. In contrast, estimated regional prevalence is lower in Western and Central Europe and North America (0.3% in adults). In this region, unprotected sex between men continues to dominate patterns of HIV transmission, though HIV prevalence among IDU varies by country, with the highest percentages in Estonia (48%), Latvia (27%), and Romania (21%) in 2015 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016b}. Although IDU account for an estimated 0.2-0.5% of the world's population, they comprise approximately 5-10% of all people living with HIV {Mathers 2008}, {United Nations Office on Drugs and Crime (UNODC) 2013}.

SI.1.3. Demographics of the Population in the Authorized Indication

SI.1.3.1. HIV Infection in Children

Worldwide, 2.1 million (95% CI: 1.7-2.6 million) children (< 15 years) were living with HIV in 2016, accounting for a substantial proportion of existing infections in Western and Central Africa (9.0%) and Eastern and Southern Africa (6.7%) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018g}. Estimates of prevalence among children were unavailable for 2016 in Western and Central Europe and North America and Eastern Europe and Central Asia (Figure SI.1).

Figure SI.1. Proportion of Individuals Infected with HIV Aged < 15 years by Geographical Region



*Data on individuals infected with HIV aged <15 years not available for Eastern Europe & Central Asia and Western & Central Europe and North America.
Source: {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018g}

Mother-to-child transmission is the main route of infection among children, by which a woman infected with HIV passes HIV to her child through pregnancy, childbirth, or breast milk. If the mother has access to antiretroviral therapy (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) 2016a}. Expansions in ART and infant feeding-based prevention services are primarily responsible for the observed declines in the number of newly infected children {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016a}. It is estimated that since 1995, ART and prophylaxis to women living with HIV while pregnant or breastfeeding prevented 1.6 million children from acquiring HIV infection worldwide, with over 80% of those infections prevented between 2010 and 2015. Approximately 48% of all children who acquired HIV infection in 2016 were living in Eastern and Southern Africa, followed by Western and Central Africa (38%), Asia and Pacific (9%), Latin America (1%), and Middle East and North Africa (1%) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018g}. The greatest reductions in HIV incidence among children between 2010 and 2016 were observed in Eastern and Southern Africa (55%), followed by Latin America (38%), Asia and Pacific (38%), and West and Central Africa (33%) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018g}. However, the Middle East and North Africa region has yet to see a significant reduction in the number of children newly infected. This is likely attributable to the rates of mother-to-child transmission remaining high in the region (30%) compared to the global rate of only 10%, which decreased from 20% in 2010 {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017c}.

SI.1.3.2. HIV Infection by Gender

Women represent about half of all patients living with HIV worldwide, and HIV incidence rates among adult women have not decreased since 2011. Gender inequalities, differential access to services, and sexual violence contribute to increased infection risk, particularly in developing regions of the world. Women account for 60% of adult infections in Eastern and Southern Africa, 57% in Western and Central Africa, 50% in the Caribbean, 44% in Eastern Europe and Central Asia, 37% in Middle East and North Africa, 37% in Asia and Pacific, 31% in Latin America, and 24% in Western and Central Europe and North America {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018f}. Young women (aged 15 to 24 years) accounted for 21% of new adult HIV infections in 2016 and are globally twice as likely to become infected compared to men {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018f}.

SI.1.3.3. HIV Infection by Age

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}. With an increase in life expectancy, younger HIV patients are projected to live several decades accessing treatment, 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) {Mahy 2014}, {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017b}. UNAIDS reports that this trend is largely due to the success of ART, decreases in HIV incidence among adults below the age of 50, and those above 50 having similar risk behaviors as those who are younger {UNAIDS 2013}.

SI.1.4. Main Existing Treatment Options

Standard of care for the treatment of HIV-1 infection uses combination ART to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. For ART-naive HIV infected patients, current European treatment guidelines recommend that initial therapy consist of 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) with an integrase strand transfer inhibitor (INSTI) or the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV) or the boosted protease inhibitor (PI) darunavir (DRV) {European AIDS Clinical Society (EACS) 2017}. In the United States (US), recommended initial ART regimens for HIV infected patients comprise 2 NRTIs plus an INSTI {U.S. Department of Health & Human Services (DHHS) 2018}. Virologically suppressed HIV infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification.

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 acquired immune deficiency syndrome (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. It is therefore difficult to provide frequency estimates of adverse events among the undiagnosed and untreated HIV population, which are also likely to differ substantially by geography, reflecting local conditions {Bradley 2014}, {Hamers 2008}. Although no effective cure currently exists, ART administered at an early enough stage can dramatically improve an HIV patient's prognosis, decreasing morbidity, mortality, and the risk of spreading the infection to others {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 2013}.

SI.1.5.1. Mortality and Morbidity

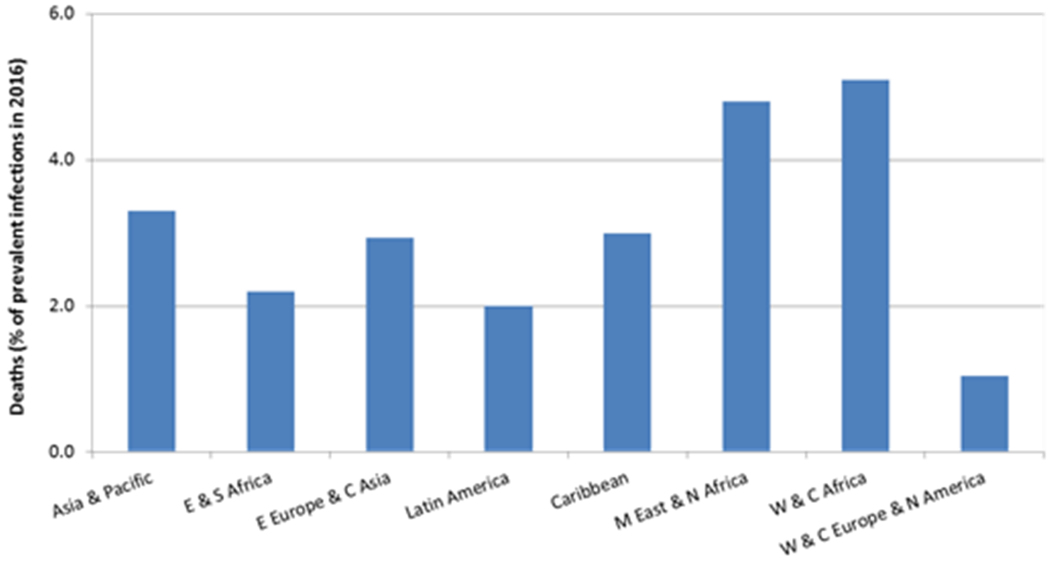
Access to effective treatment varies considerably, accounting for different rates of mortality by region. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of scaled up ART and the steady decline in HIV incidence since the peak in 1997. In 2016, this decline continued, with evidence that the drop in the number of people dying from AIDS-related causes is accelerating in several countries. In 2016, 1.0 million (95% CI: 830,000-1.2 million) people died from AIDS-related causes worldwide, representing a 32% decline compared to 2010 when 1.5 million (95% CI: 1.3-1.7 million) deaths occurred {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017c}. The leading cause of death

among those living with HIV continues to be tuberculosis, which accounts for around one in three AIDS-related deaths {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2017}. There was a 37% reduction of deaths among women between 2010 and 2015 compared to a 22% reduction among men. This is likely reflective of the varying rates of treatment coverage by gender (women: 60%; men: 47%).

The number of people dying from AIDS-related causes in Eastern and Southern Africa declined by more than 40% from 2010 to 2016, although the region still accounted for 42% of all the people dying from AIDS in 2016. Declines in AIDS-related deaths between 2010 and 2016 also occurred in Western and Central Europe and North America (31% decline), Asia and Pacific (29%), the Caribbean (28%), Western and Central Africa (21%), and Latin America (12%) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a}. Two other regions, however, experienced significant increases in mortality from AIDS: Eastern Europe and Central Asia (25% increase) and Middle East and North Africa (15%) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a}. In conjunction with the dramatic reduction of pediatric incidence of HIV infection, the number of AIDS-related deaths among children has decreased by 43% between 2010 and 2016, with even greater reductions observed in Eastern and Southern Africa (55%) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018b}. Figure SI.2 provides regional variations in HIV related mortality (deaths as a percentage of prevalent HIV infections in 2016) {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a}.

Following the introduction of Highly Active Antiretroviral Therapy (HAART), mortality rates declined due to decreases in both non-AIDS and AIDS-related deaths, although the proportion of deaths associated with non-AIDS-related diseases has increased in patients on ART {Weber 2013}, {Palella 2013}, {Ingle 2014}. Common causes of non-AIDS-related deaths are non-AIDS-related malignancies, liver failure, non-AIDS-related infections, substance use-related, suicide, and myocardial infarction {Weber 2013}.

Figure SI.2. Regional Variation in HIV-Related Mortality



Source: {The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018a}

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 {Deeks 2013}, {Hsue 2016}, {Hirschhorn 2012}, {Balderson 2013}. 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 suicide ideation)
- Neurocognitive disorders
- Pulmonary disease (i.e., chronic obstructive pulmonary disease)

- Renal disease
- Other sexually transmitted diseases
- Some non-HIV-related malignancies (i.e., liver, cervical, anal, and Hodgkin's lymphoma)
- Tuberculosis

SI.2. HBV Infection

SI.2.1. Incidence

The incidence of new hepatitis B virus (HBV) infection varies by geographical region, with the highest incidence in regions with high prevalence (see section SI.2.2). Incidence of HBV infection has decreased considerably due to the widespread use of the HBV vaccine in infancy, which had an estimated global coverage of 84% in 2015. However, transmission from mother-to-child and between young children remains high in geographies where HBV is endemic and accounts for the majority of new infections {World Health Organization (WHO) 2017}, {Voiculescu 2015}. In geographies of low incidence, such as the European region and region of the Americas, transmission mainly occurs among adolescents and adults via sexual contact and injection drug use {MacLachlan 2015}, {Trepo 2014}. The implementation of universal precautions and improved methods of blood donor screening significantly reduced HBV transmission in healthcare settings, contributing to the decrease of incidence in these regions {Trepo 2014}. Some key illustrative figures for the incidence of infection in Europe are as follows {Roure 1995}:

- The lowest rate of infection was in Northern European countries at less than 1/100,000 per year
- Southern European countries had an incident rate of around 6/100,000 per year
- Central European countries had a markedly higher incidence of infection at approximately 20/100,000 per year

SI.2.2. Prevalence

Worldwide, 257 million (95% CI: 199-368 million) people were estimated to be living with HBV infection in 2015, accounting for 3.5% (95% CI: 2.7-5.0%) of the total population. Global prevalence varies widely, with the largest burden of disease in the Western Pacific and Africa regions (6.2% and 6.1%, respectively). These two regions alone comprise 68% of the total infected population. Regions with intermediate prevalence are the Eastern Mediterranean and South-East Asia regions (3.3% and 2.0%, respectively); and the lowest prevalence is found in the European region and region of the Americas (1.6% and 0.7%, respectively). Overall, the majority of those currently living with HBV were infected before 5 years of age and were born prior to the widespread use of the HBV vaccine in infancy (between 1980 and early 2000's). (Table SI.2; {World Health Organization (WHO) 2017}, {Schweitzer 2015}).

Since the introduction of the HBV vaccine, worldwide prevalence among children (5 years old and below) decreased from 4.7% to 1.3%, contributing to the overall decline in prevalence {World Health Organization (WHO) 2017}. However, some developing countries, where

implementation of vaccination programs is challenging, have not experienced as significant a decline. For example, although the European region has an overall low prevalence of 1.6% (95% CI: 1.2-2.6%), Eastern European countries have been found to have higher prevalence compared to Western European countries {Schweitzer 2015}, {Duffell 2015}, {Ott 2017}, {Zampino 2015}. Additionally, prevalence in some low endemic geographies is increasing due to migration from areas of high or intermediate prevalence {MacLachlan 2015}.

Table SI.2. Regional Prevalent Cases of HBV Infection in 2015

	Number of Prevalent Cases (n; 95% CI) Overall	Prevalent Cases (%; 95% CI) Overall	Prevalent Cases (%; 95% CI) Children[a]
Africa Region	60 million (45-84 million)	6.1 (4.6-8.5)	3.0 (2.0-4.7)
Region of the Americas	7 million (4-16 million)	0.7 (0.4-1.6)	0.2 (0.1-0.5)
Eastern Mediterranean Region	21 million (17-28 million)	3.3 (2.6-4.3)	1.6 (1.2-2.1)
European Region	15 million (11-23 million)	1.6 (1.2-2.6)	0.4 (0.2-0.8)
South-East Asia Region	39 million (29-77 million)	2.0 (1.5-4.0)	0.7 (0.5-1.6)
Western Pacific Region	115 million (93-140 million)	6.2 (5.1-7.6)	0.9 (0.6-1.3)
Total	**257 million (199-368 million)**	**3.5 (2.7-5.0)**	**1.3 (0.9-2.2)**

a Prevalence of Hepatitis B Surface Antigen (HBsAg) among children aged 5 years and younger.
Source: {World Health Organization (WHO) 2017}

SI.2.3. Demographics of the Population in the Authorized Indication

SI.2.3.1. HBV Infection by Age

Age at the time HBV is contracted is a major predictor of chronic infection. Perinatal transmission rates range from 10% to 90%, with 40% to 90% of infants infected at birth developing chronic infection {Kew 2010}. Infection during childhood (5 years old and below) is also likely to develop into chronic infection (50%), and is considered a major indicator by World Health Organization (WHO) for measuring success in abating HBV infection worldwide {Kew 2010}, {World Health Organization (WHO) 2017}. Horizontal transmission between children or other close contacts is the primary source of infection at this age. Prevalence among children is highest in the Africa region (3.0% [95% CI: 2.0-4.7%]) and the Eastern Mediterranean region (1.6% [95% CI: 1.2-2.1]) (Table SI.2; {World Health Organization (WHO) 2017}).

Contracting HBV in adulthood is less likely to result in chronic infection and is more common in areas where HBV prevalence is low. Major modes of transmission include high-risk behaviors including sexual contact with multiple partners, men who have sex with men, and injection drug use, and to a lesser degree, hospital acquired infection {Trepo 2014}, {Kew 2010}. In the EU, 33.4% of all HBV cases (acute and chronic) were among adults 25-34 years old from 2006 to 2012. The prevalence of reported chronic HBV cases among adults in this age group was the highest (approximately 30 per 100,000), while the prevalence among age groups greater than 45 years old were all below 10 per 100,000. The age distribution of reported acute cases was

similar to that of chronic cases, though prevalence of acute cases is much lower compared to chronic (less than 5 per 100,000 among all age groups) {Duffell 2015}.

SI.2.3.2. HBV Infection by Gender

Worldwide, HBV prevalence among men (3.9%) was slightly higher compared to women (3.5%) in 2005 {Ott 2012}.

SI.2.4. Main Existing Treatment Options

The goal of therapy for chronic hepatitis B is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC), and death {European Association for the Study of the Liver (EASL) 2017}. This goal can be achieved if HBV replication can be suppressed in a sustained manner. Drugs available for the treatment of chronic hepatitis B include interferon alpha (IFN), pegylated interferon alpha (PEG-IFN) and nucleoside/ nucleotide analogues (NAs). NAs for HBV therapy directly inhibit the HBV reverse transcriptase polymerase and can be classified into nucleosides (i.e., lamivudine, telbivudine, and entecavir) and nucleotides (i.e., adefovir dipivoxil, tenofovir disoproxil fumarate, and tenofovir alafenamide). For treatment-naïve patients, current treatment guidelines recommend the long-term administration of a potent NA with high barrier to resistance (e.g., entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide) {European Association for the Study of the Liver (EASL) 2017}.

SI.2.5. Natural History of the Indicated Condition including Mortality and Morbidity

The course of HBV infection is highly variable and depends on several factors, including age at infection, immune status and how quickly the infection is recognized. Two distinct phases can be described: acute and chronic. The acute phase of HBV infection begins between 6 and 24 weeks post infection. Much acute infection is asymptomatic, but this phase may be accompanied by nausea, vomiting, anorexia, headache, jaundice and increased aminotransferase levels. In a small proportion of cases, fulminant hepatitis occurs, but the acute phase of infection is very rarely fatal. Patients who successfully recover from the acute phase of illness develop permanent immunity to future infection, detectable in serum by the presence of anti-hepatitis B antibodies. Table SI.3 summarizes the main features of acute HBV infection in adults and neonates {World Health Organization (WHO) 2002}.

Table SI.3. Course of Acute HBV Infection in Adults and Neonates

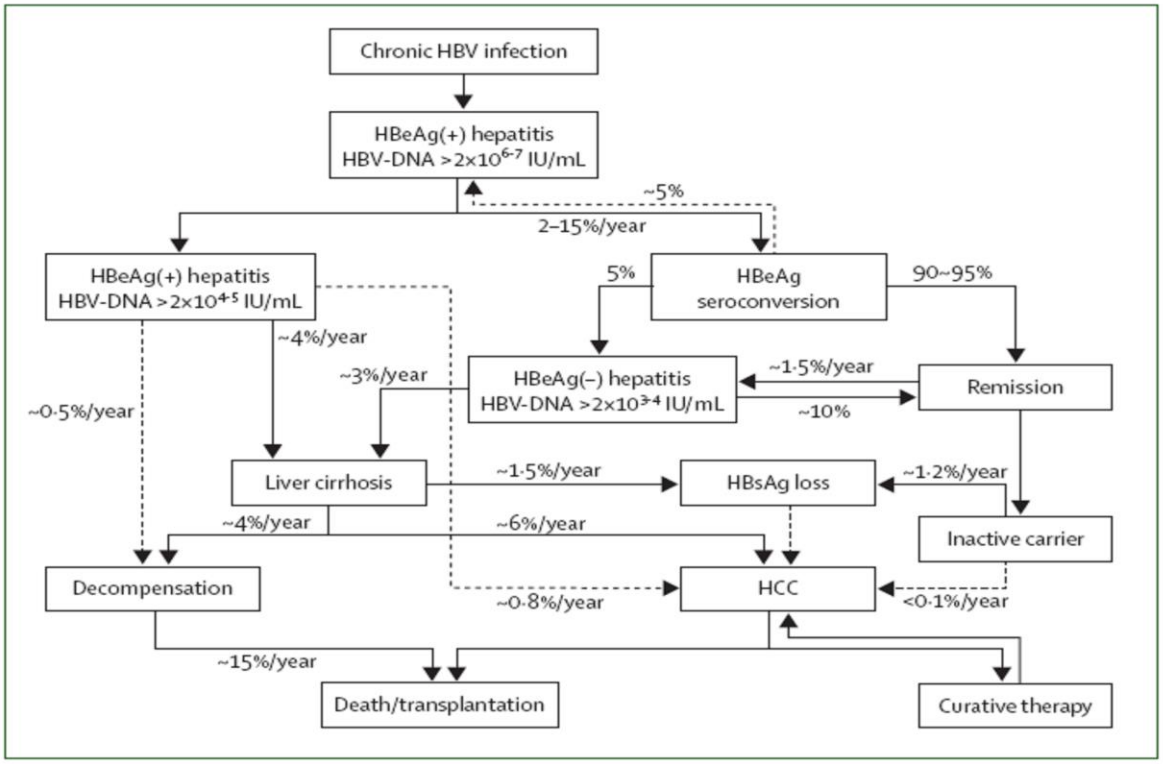
Feature	Adults	Neonates
Asymptomatic	50-70%	~90%
Symptomatic	30-50%	~10%
Fulminant hepatitis	<1%	<1%
Full recovery with permanent immunity (anti-HBs antibodies)	~90%	~10%

Patients who do not fully recover from the acute phase will go on to experience the chronic phase of HBV infection. This is characterized by progressive inflammation of the liver and it can take decades for symptoms to develop. During this period, distinct immunological features include the serum presence of the hepatitis B surface antigen (HBsAg). All patients with serum HBsAg are potentially infectious and all patients with chronic HBV are HBsAg positive. Every year, ~ 2% of chronic HBV patients terminate active infection and become HBsAg negative. Patients who remain infected experience gradually declining liver function and frequently develop liver cirrhosis and HCC.

SI.2.5.1. Morbidity and Mortality

Liver cirrhosis and HCC are serious complications associated with chronic HBV infection in its more advanced stages, accounting for 96% of deaths due to viral hepatitis in 2015 {World Health Organization (WHO) 2017}. Cirrhosis, liver failure, and/or HCC are expected to develop in 15% to 40% of HBV infected individuals {Lavanchy 2004}. Approximately 2% to 10% of chronic hepatitis B (CHB) patients progress to cirrhosis each year, and 5% to 10% of cirrhotic patients develop evidence of hepatic decompensation or HCC each year {Sherman 2007}. In patients with CHB, the 5 year cumulative incidence of developing cirrhosis is 8% to 20%. The 5 year cumulative incidence of decompensation is 20%. The 5 year survival rate is 80% to 86% for compensated cirrhosis and 14% to 35% for decompensated cirrhosis {European Association For The Study Of The Liver 2009}. A schematic showing the possible outcomes of HBV infection is shown in Figure SI.3.

Figure SI.3. Possible Outcomes of Chronic Hepatitis B



Source: {Liaw 2009}

Cirrhosis

Progression to cirrhosis is more frequent in older patients, men, alcohol abusers, and those with hepatitis B e antigen (HBeAg) negative disease. After cirrhosis develops, the yearly risk of decompensation (manifested as ascites, jaundice, portal hypertension, and/or variceal bleeding) is approximately 6% {The Institute of Hepatology 2004}. Typical changes in laboratory values after progression to cirrhosis include decreased serum albumin, prolonged prothrombin time, and decreased platelet counts {European Association For The Study Of The Liver 2009}. Approximately 10% to 30% of patients with CHB have acute ALT flares due to destruction of infected hepatocytes by the immune system {The Institute of Hepatology 2004}.

Hepatocellular carcinoma

Patients with CHB are 100 times more likely to develop HCC than those who resolve an acute HBV infection. HCC is likely to develop 25 to 30 years after the acute infection, when hepatocytes damaged through the immune response regenerate. The mortality rate for HCC is very high; the 5-year survival rate is only 5% to 6% {The Institute of Hepatology 2004}.

The worldwide prevalence of HCC largely reflects the distribution of HBV infection, and the incidence has increased, primarily due to new viral infections, and is the sixth most common cancer worldwide {MacLachlan 2015}. Among cirrhotic patients with CHB, the annual incidence of HCC is 2% to 5% {European Association For The Study Of The Liver 2009}. HBV accounts for up to 80% of primary liver cancers, and it is second only to tobacco as a leading cause of human cancer {Zuckerman 2007}, {The Institute of Hepatology 2004}.

Liver transplantation

Cirrhosis and HCC are among the leading indications for liver transplantation {Kim 2009}. According to the US Organ Procurement and Transplantation Network, 1 year survival rates following liver transplantation for cirrhosis or HCC are 85% to 90%. At 3 years, survival rates range from 68% for HCC to 77%–85% for cirrhosis, and at 5 years drop to 54% for HCC and 70%–80% for cirrhosis {Organ Procurement and Transplantation Network 2009}. Without prophylaxis, >80% of patients who receive liver transplants for HBV related illness will have recurrent infection.

SI.2.6. Important Co-morbidities

Below is a list of important conditions that have evidence of higher risk among HBV patients and/or those accessing antiviral treatment for HBV:

- Renal Disorders {di Belgiojoso 2002}, {Worobetz 2000}, {Liu 2018}

  Membranous glomerulonephritis (GN)

  Membranoproliferative GN

  IgA nephropathy

Hepatorenal syndrome

Fanconi syndrome

- Bone Disorders

  Fractures (in patients with severe liver disease) {Biver 2017}

  Reduced bone mineral density {Tsuneoka 1996}, {Schiefke 2005}, {Gonzalez-Calvin 2004}, {Gallego-Rojo 1998}, {Gill 2011}

  Osteoporosis {Gonzalez-Calvin 2004}, {Chen 2015}, {Gallego-Rojo 1998} {Fung 2011}

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

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

Key Safety Findings from Non-clinical Studies	Relevance to Human Usage
Nonclinical safety pharmacology studies reveal no special hazard for humans (studies 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 tenofovir and TDF in nonclinical studies. Increases in serum creatinine, blood urea nitrogen, 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, hypophosphatemia and proximal renal tubulopathy (PRT) (including Fanconi syndrome) have been reported with the use of TDF in clinical practice (Viread summary of product characteristics [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. In clinical studies of HIV-1 infected patients 2 to < 18 years of age and HBV infected patients 2 to < 18 years of age, small decreases in median BMD Z-scores were observed following treatment with TDF. The long-term clinical relevance of these observations is unknown. Osteomalacia (infrequently contributing to fractures) may be associated with PRT (Viread 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. TDF 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.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

SIII.1.1. Clinical Trial Exposure for Tenofovir DF in Subjects with HIV Infection

The tables in this section present exposure data for TDF in subjects with HIV-1 infection from the following completed studies:

- GS-98-902, GS-99-903, GS-99-903e, GS-99-907, GS-99-908, GS-01-926, GS-01-927, GS-01-934, GS-US-104-0235, GS-02-1016, GS-02-1015, GS-02-1008, GS-99-910, GS-US-104-0321, GS-US-104-0352 and expanded access programs (EAPs)

Data from the following HIV pediatric studies are also presented separately:

- GS-01-926, and GS-01-927, GS-US-104-0321 and GS-US-104-0352

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

Duration of Exposure	Persons	Person-days
≥ 1 day	5247	2,060,051
> 30 days	4781	2,052,960
> 90 days	3787	1,991,280
> 180 days	2502	1,817,345
> 1 year	1444	1,533,327
> 2 years	749	1,131,843
> 3 years	358	773,848
> 4 years	229	617,453
> 5 years	207	581,926
> 6 years	191	549,917
> 7 years	106	350,378
> 8 years	90	307,557
> 9 years	78	269,639
> 10 years	6	22,831

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

	Persons		Person-days	
Age Group	**Male**	**Female**	**Male**	**Female**
< 12 years	54	42	93,812	90,138
12-17 years	44	59	33,238	44,070
18-30 years	226	102	157,023	84,621
31-40 years	1510	417	617,196	175,723
41-50 years	1591	232	457,025	77,430
51-65 years	736	62	189,830	21,354
66-75 years	49	5	8517	500
> 75 years	1	0	576	0
Missing Age	13	3	685	678
Missing Sex & Age	101		7747	

Table SIII.3. Exposure by Racial Origin in Subjects with HIV-1 Infection

Racial Group	**Persons**	**Person-days**
Caucasian	2412	1,087,209
Black	621	280,639
Hispanic	377	119,247
Asian	28	9906
Other	174	276,835
Not Collected[a]	1635	286,311

a Only two expanded access program studies (US and Canada) collected race information

Table SIII.4. Exposure in Special Populations with HIV-1 Infection

Special Population		**Persons**	**Person-days**
Renal Impairment[a]	Mild	94	48,624
	Moderate/ Severe	5	1030

a Pediatric studies GS-US-104-0321 and GS-US-104-0352 were not evaluated for renal impairment subgroup analysis

Table SIII.5. Duration of Exposure in Pediatric Subjects with HIV-1 Infection[a]

Duration of exposure	2-11 years		12-17 years	
	Persons	Persons-day	Persons	Persons-day
≥ 1 day	96	183,950	99[b]	76,886
> 30 days	94	183,934	96	76,865
> 90 days	93	183,892	96	76,865
> 180 days	92	183,773	90	75,982
> 1 year	81	180,199	62	68,411
> 2 years	76	177,460	43	57,053
> 3 years	67	169,001	26	41,449
> 4 years	58	157,949	16	28,900
> 5 years	51	146,574	6	12,753

a Pediatric studies included: GS-US-104-0352, GS-US-104-0321, GS-01-926, and GS-01-927
b The data in Table SIII.2 was based an output including studies and EAPs; data in this table is based on an output from pediatric studies only. The small difference in number of subjects in the HIV 12-17 Years group between the 2 tables is caused by this difference in data source.

SIII.1.2. Clinical Trial Exposure for Tenofovir DF in Subjects with HBV Infection

The tables in this section present exposure data for TDF (up to 31 July 2021) in adult and pediatric subjects with HBV infection from the following studies:

- Completed studies GS-US-174-0102, GS-US-174-0103, GS-US-174-0106, GS-US-174-0108, GS-US-174-0115, GS-US-174-0121, GS-US-174-0123, GS-US-174-0141, GS-US-174-0149, GS-EU-174-0160, GS-US-203-0101, GS-US-330-1401, GS-US-283-1062, GS-EU-174-1403, and GS-US-174-0144 (Week 192 milestone)
- Ongoing blinded studies GS-US-320-0108, GS-US-320-0110 and GS-US-320-4018
- Ongoing open label studies GS-US-320-3912

Data from the following HBV pediatric studies are also presented separately:

- GS-EU-174-1403, GS-US-174-0115 and GS-US-174-0144

Table SIII.6. Duration of Exposure in Subjects with HBV Infection

Duration Of Exposure	Ongoing Blinded Studies (All subjects exposed to blinded treatment)		Completed, Stopped or Ongoing Open-Label/Unblinded Studies (Subjects exposed to TDF)	
	Persons	Person-days	Persons	Person-days
≥ 1 day	1632	1,375,314	2610	2,960,148
> 30 days	1617	1,375,149	2579	2,959,810
> 90 days	1606	1,374,479	2561	2,958,694
> 180 days	1597	1,373,279	2534	2,954,779
> 1 year	1569	1,365,724	1912	2,752,198
> 2 years	964	967,820	1573	2,557,588
> 3 years	0	0	880[a]	1,912,267
> 4 years	0	0	659	1,626,866
> 5 years	0	0	469	1,311,282
> 6 years	0	0	430	1,232,830

a Due to Study GS-US-330-1401 status change in 2019, the Viread exposure duration was reduced in 4 subjects. These 4 subjects were moved to the less than 3 years duration category.

Table SIII.7. Exposure by Age Group and Gender in Subjects with HBV Infection

	Ongoing Blinded Studies (All subjects exposed to blinded treatment)				Completed, Stopped or Ongoing Open-Label/Unblinded Studies (Subjects exposed to TDF)			
	Persons		Person-days		Persons		Person-days	
Age Group	Male	Female	Male	Female	Male	Female	Male	Female
2-11 years	0	0	0	0	49	35	74,730	52,208
12-17 years	0	0	0	0	85	37	84,760	34,049
18-30 years	260	120	221,509	95,695	335	166	406,874	144,727
31-40 years	345	147	292,497	123,626	435	195	497,052	172,363
41-50 years	274	140	233,723	121,494	452	209	584,213	232,570
51-65 years	174	153	143,882	127,605	367	187	424,167	209,974
66-75 years	9	9	8190	7092	38	16	31,988	9134
> 75 years	1	0	1	0	3	1	1003	336

Table SIII.8. Exposure by Racial Origin in Subjects with HBV Infection

Racial Origin	Ongoing Blinded Studies (All subjects exposed to blinded treatment)		Completed, Stopped or Ongoing Open-Label/Unblinded Studies (Subjects exposed to TDF)	
	Persons	Person-days	Persons	Person-days
Caucasian	254	213,034	898	1,368,220
Black	13	9023	92	107159
Asian	1354	1,144,500	1541	1,381,848
Pacific Islander	6	5398	36	40,562
Other	5	3359	43	62,359

Table SIII.9. Exposure in Special Populations with HBV Infection

Special Population		Ongoing Blinded Studies (All subjects exposed to blinded treatment)		Completed, Stopped or Ongoing Open-Label/Unblinded Studies (Subjects exposed to TDF)	
		Persons	Person-days	Persons	Person-days
Renal Impairment[a]	Mild	152	121,628	304	298,677
	Moderate/ Severe	2	1025	16	10,827

a Pediatric studies GS-US-174-0115 and GS-US-174-0144 were not evaluated for renal impairment subgroup analysis

Table SIII.10. Duration of Exposure in Pediatric Participants with HBV Infection[a]

Duration of exposure	2-11 years		12-17 years	
	Persons	Persons-day	Persons	Persons-day
≥ 1 day	84	126,938	122	118,809
> 30 days	82	126,909	122	118,809
> 90 days	82	126,909	121	118,756
> 180 days	81	126,789	118	118,257
> 1 year	80	126,565	112	116,684
> 2 years	77	125,137	88	103,722
> 3 years	71	119,871	56	76,219
> 4 years	41	79,683	5	8,562
> 5 years	23	50,311	1	1,854

a Pediatric studies included: GS-EU-174-1403, GS-US-174-0144, and GS-US-174-0115

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
Pregnant females	Limited information on the use in this patient population.	Yes
Females who are breastfeeding	Limited information on the use in this patient population.	Yes
Inadequate renal function: Serum creatinine ≥ 1.5 mg/dL and/or calculated CL_{cr} < 70 mL/min to < 50 mL/min according to the Cockcroft-Gault formula	Tenofovir is primarily renally excreted by a combination of glomerular filtration and tubular secretion. Tenofovir pharmacokinetics (PK) are substantially altered in subjects with moderate and severe renal impairment.	Yes Safety in patients with renal impairment is considered to be missing information.
Patients receiving ongoing therapy with any of the following (must be discontinued at least 30 days prior to the baseline visit and for the duration of the study period): • Nephrotoxic agents • Agents that compete for elimination via active tubular secretion • Immunomodulators (e.g., corticosteroids, etc.), investigational agents, or agents susceptible of modifying renal excretion	Renal toxicity is an important identified risk for TDF.	No Rationale: Collection of further safety data for patients receiving these particular classes of drugs is not considered warranted, as the risk of coadministration can be predicted (e.g., risk of additive nephrotoxicity). The Viread SmPC contains text recommending avoiding use of nephrotoxic agents with TDF, and guidance that coadministration of TDF with medicinal products that reduce renal function or compete for active tubular secretion via transport proteins hOAT 1, hOAT 3 or MRP-4 (e.g. cidofovir) may increase serum concentrations of tenofovir and/or the coadministered medicinal products, and that given that tacrolimus can affect renal function, close monitoring is recommended when it is coadministered with 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[a]	Discussion of Implications for Target Population
Which are rare	A total of 9489 subjects have been exposed to TDF across the HIV and HBV clinical trial programs.	The clinical trial population is large enough to detect rare adverse drug reactions (ADRs). ADRs with a frequency of greater than 1 in 2500 could be detected if there were no background incidence.
Due to prolonged exposure	1238 subjects have been exposed to TDF for more than 3 years in the TDF clinical trial programs. 621 subjects have been exposed to TDF for more than 6 years in the TDF clinical trial programs.	No ADRs specifically associated with prolonged exposure to TDF have been identified in the clinical trial programs.
Due to cumulative effects	1238 subjects have been exposed to TDF for more than 3 years in the TDF clinical trial programs. 621 subjects have been exposed to TDF for more than 6 years in the TDF clinical trial programs.	No cumulative effects to TDF have been identified in the clinical trial programs.
Which have a long latency	1238 subjects have been exposed to TDF for more than 3 years in the TDF clinical trial programs. 621subjects have been exposed to TDF for more than 6 years in the TDF clinical trial programs.	No ADRs to TDF with a long latency have been identified in the clinical trial programs.

a Table includes the number of subjects exposed to TDF in completed studies and ongoing open-label/unblinded studies (subject exposure in ongoing blinded studies is not included)

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[a]	Considered to be Missing Information
Elderly patients	126 subjects (65,421 person-days) aged above 65 years have been exposed to TDF across the HIV and HBV clinical trial programs.	No Rationale: Safety in elderly patients is monitored on an ongoing basis through routine pharmacovigilance activities and data have been presented periodically in the Viread periodic safety update report (PSUR). No safety concerns regarding use of TDF in elderly patients have been identified.
Pregnant women	Pregnant women were excluded from enrolling in clinical studies. As of 31 March 2018, there were 90 cases of pregnancy during treatment with TDF in Gilead-sponsored clinical studies.	No Rationale: Based on the Antiretroviral Pregnancy Registry report (data to 31 July 2024), sufficient numbers of first trimester exposures (TDF [n=5076]) have been monitored with no increase in birth defects detected. Safety in pregnant women is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in PSURs/PBRERs. Viread's SmPC contains guidance on use during pregnancy and lactation.
Breastfeeding women	Breastfeeding women were excluded from enrolling in clinical studies. As of 31 March 2018, there was 1 case of breastfeeding during treatment with TDF in Gilead-sponsored clinical studies.	No Rationale: Based on the Antiretroviral Pregnancy Registry report (data to 31 July 2024), sufficient numbers of first trimester exposures (TDF [n=5076]) have been monitored with no increase in birth defects detected. Safety in breastfeeding women is monitored on an ongoing basis through routine pharmacovigilance and data are presented periodically in PSURs/PBRERs. Viread's SmPC contains guidance on use during pregnancy and lactation.
Patients with hepatic impairment	Child-Pugh-Turcotte (CPT) score was not routinely documented in pivotal HBV studies. 63 subjects (61,851 person-days) with hepatic decompensation were exposed to TDF in studies GS-US-174-0108 and GS-US-174-0141 in the HBV clinical trial program.	No Rationale: 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).

Type of Special Population	Exposure[a]	Considered to be Missing Information
Patients with renal impairment	304 subjects (420,305 person-days) with mild renal impairment and 18 subjects (11,852 person-days) with moderate/ severe renal impairment have been exposed to TDF in the TDF clinical trial programs.	No Rationale: Safety in patients with renal impairment is monitored on an ongoing basis through routine pharmacovigilance activities and data will be presented periodically in the Viread PSUR/PBRERs. No safety concerns regarding the use of Viread in patients with renal impairment have been identified. Viread's SmPC contains guidance on use in patients with renal impairment.
Black HBV infected patients	105 black subjects (116,182 person-days) have been exposed to TDF in the HBV clinical trial program.	No Rationale: Safety in black HBV infected patients has been monitored on an ongoing basis through routine pharmacovigilance activities and data have been presented periodically in the Viread PSUR. No safety concerns regarding use of TDF in black HBV infected patients have been identified. No specific safety concerns are anticipated for black HBV infected patients.

a Table includes the number of subjects exposed to TDF in completed studies and ongoing open-label/unblinded studies (subject exposure in ongoing blinded studies is not included)

PART II: MODULE SV- POST-AUTHORIZATION EXPERIENCE

SV.1. Post-Authorization Exposure

SV.1.1. Method Used to Calculate Exposure

Sales Data

Patient exposure to marketed Viread tablets (150 mg, 200 mg, 250 mg and 300 mg) has been estimated from sales data; the number of bottles sold cumulatively was multiplied by 30 to provide the number of tablets sold. As tenofovir DF is taken as a once daily dose, the total number of tablets was divided by 365.25 to provide patient-years of treatment.

For Viread 300 mg tablets it is not possible to separate postmarketing exposure by HIV and HBV indication, since postmarketing exposure is based on sales data and the same tablets are used for both the HIV and the HBV indication. Viread reduced strength tablets are indicated for the treatment of HIV infected pediatric patients only.

It is not possible to calculate the patient-years exposure based on sales data for the oral powder as the amount of powder administered is dependent on body weight.

It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure, due to the accumulation of drug stocks at pharmacies/distributors and wastage.

Prescription Data

Estimates of the demographics of patients exposed to Viread in five major European countries (France, Germany, Italy, Spain and UK) were obtained from prescription data from the following sources:

IMS/Groupement pour l'Élaboration et la Réalisation de Statistiques (GERS): IMS 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 IMS data.

Ipsos Monitor: The Ipsos Healthcare HIV EU Therapy Monitor study is a syndicated, annual (previously bi-annual) diary study involving HIV treating physicians and data has been obtained from April - June 2019. A total of 209 HIV treating physicians are involved across the five major 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 12 patients they see during the fieldwork period. These patients could

be initiating, switching or maintaining, as well as patients who have never been treated or those who are not currently receiving ARV therapy. In the five major European countries (19Q2), this dataset consists of 1624 patient records (all of whom are currently receiving ARV treatment because we no longer collect untreated patient record forms).

SV.1.2. Exposure

SV.1.2.1. Exposure Based on Sales Data

Cumulative patient exposure to all Viread tablet formulations since first marketing approval in United States on 26 October 2001 to 31 March 2025 is estimated to be 6,454,309 patient years of treatment.

Cumulatively, a total of 36,858 bottles of Viread oral powder have been sold since first marketing approval in the United States on 18 January 2012 to 31 March 2025.

Further information on cumulative patient exposure by geographic areas is provided in the PSUR/PBRER for Viread.

SV.1.2.2. Exposure Based on Prescription Data

Estimates of the demographics of HIV infected patients exposed to Viread in the EU5 countries, based on prescription data, indicate that 40% of the patients were male, and all the patients were aged ≥ 46 years. Further details on the demographics of patients exposed to Viread are available in the Viread PSUR/PBRER.

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 TDF 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 for TDF since the submission of the last EU-RMP.

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

Table SVII.1. Important Identified Risks and Missing Information: Reason for Removal

Safety Concern Removed	Reason for Removal from List of Safety concerns
Important Identified Risks	
Renal toxicity	Renal toxicity is proposed to no longer be considered an important identified risk for the following reasons: There are no outstanding additional risk minimization measures. Renal messages are included in the current European treatment guidelines for HIV infection {European Aids Clinical Society (EACS) 2022} {Bamford 2015} and renal monitoring recommendations are provided in the EU SmPCs for Viread. Thus, the additional PV activity of 'Monitoring of reversibility of renal tubulopathy in clinical trials' for the identified risk of renal toxicity is proposed to be removed, as this activity is not a safety study. Given that the management of this risk is fully integrated into standard clinical practice (through inclusion in treatment guidelines), the risk is considered fully characterized and appropriately managed. Renal toxicity is proposed to be removed from the list of safety concerns in the EU-RMP. Renal toxicity will continue to be monitored through routine pharmacovigilance and any new significant safety information for renal toxicity will be summarized and presented in relevant sections of future PSUR/PBRERs as requested in the PRAC assessment report for Viread (PSUSA (EMEA/H/C/PSUSA/00002892/202303).
Bone events due to proximal renal tubulopathy/loss of BMD	Bone events due to proximal renal tubulopathy/loss of BMD is proposed to no longer be considered an important identified risk for the following reasons: There are no outstanding additional risk minimization measures or additional PV activities for this risk. Bone effects are provided in the EU SmPCs for Viread and bone effects and screening recommendations are included in the current 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 List of Safety concerns
	Bone events due to proximal renal tubulopathy/loss of BMD is proposed to be removed from the list of safety concerns in the EU-RMP. 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 in the PRAC assessment report for Viread (PSUSA (EMEA/H/C/PSUSA/00002892/202303).
Missing Information	
Safety in pregnancy and lactation	Based on the Antiretroviral Pregnancy Registry report (31 Jul 2024) for TDF, sufficient numbers of first trimester exposures (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 or lactation is needed to further characterize this risk. According to the Viread EU SmPC, more than 1000 pregnancy outcomes indicate no malformations or foetal/neonatal toxicity associated with TDF. Tenofovir is excreted in human milk at very low levels and exposure of infants through breast milk is considered negligible. In humans, samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower that the tenofovir IC_{50} {Benaboud 2011}. There is adequate information in Section 4.6 of Viread EU SmPC for the healthcare professional to make an informed decision regarding use of TDF in pregnancy and 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}, therefore, is considered appropriately managed.
Safety in patients with renal impairment	Recommended by PRAC for removal of this missing information and consistent with removal of the important identified risk of renal toxicity as there are no additional risk minimization measures and no remaining additional PV activities to address this concern.

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

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

In the PRAC assessment report for the PSUR/PBRER (EMEA/H/C/PSUSA/00002892/202303), covering the reporting period from 01 April 2020 to 31 March 2023, as the important identified risks of renal toxicity and bone events due to Proximal Renal Tubulopathy/Loss of BMD have been removed, the Rapporteur suggested removal of corresponding follow-up questionnaires, and Gilead agreed to this proposal. There are no specific adverse reaction follow-up questionnaires for any of the safety concerns.

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

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

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

V.1. Routine risk minimization measures

The routine risk minimization measures for Viread in the EU comprise of the SmPC, the package leaflet (PL) and the legal status of the product. Viread is subject to restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B [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 applicable to all of the individual safety concerns.

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

Table Part V.2. Additional Risk Minimization Activity for Important Identified Risk of Renal Toxicity

Healthcare Professional Educational Initiatives (HIV and HBV educational guides) for prescribers of TDF to pediatric patients	
Objective(s)	The HCP educational guides specific to the use of TDF in HIV-1 and HBV infected pediatric patients have been prepared to provide advice to physicians on the management of renal effects in pediatric patients. The guides also include additional information specific to use of TDF in pediatric patients on the approved indications, the management of bone effects, and information on the appropriate dosing of TDF in pediatric patients. The MAH has extended the HBV pediatric educational guide to include children aged 2 to < 12 years as well as adolescents.
Rationale for the additional risk minimization activity	Prescriber awareness of important renal management information will assist in preventing or minimizing the risk of renal toxicity in pediatric patients. Additional risk minimization measures for prescribers of adult patients have been completed and the renal safety concern in HIV-1 and HBV infected adults is now being managed through routine risk minimization activities.
Target audience and planned distribution path	Prescribers of HIV-1 and HBV infected pediatric patients via mail.

Healthcare Professional Educational Initiatives (HIV and HBV educational guides) for prescribers of TDF to pediatric patients	
Plans to evaluate the effectiveness of the interventions and criteria for success	*Drug Utilization Studies* An observational, drug utilization study of Viread in children and adolescents with HIV-1 infection (GS-EU-104-0433) was conducted to assess the effectiveness of the risk minimization measures (EU SmPC and HIV pediatric educational guide) that have been implemented post-approval of Viread in the pediatric population. The clinical study report was submitted in December 2017 (procedure number EMEA/H/C/WS1326, date of approval 17 May 2018 [CHMP Opinion]). A further drug utilization study was conducted to collect information on the effectiveness of risk minimization measures (SmPC/HBV pediatric educational guide) in HBV infected pediatric patients (GS-EU-174-0224). The clinical study report was submitted in May 2018 (procedure number EMEA/H/C/000419/II/0188), date of approval 06 September 2018 [CHMP Opinion]).
Rationale for proposing to remove additional risk minimization measure(s)	The MAH proposes to remove the additional risk minimization activities for pediatric patients (HIV and HBV pediatric educational guides) based upon the following: • The 2 drug utilization studies conducted to evaluate the effectiveness of risk minimization measures including the pediatric educational guides have been completed; the final GS-EU-104-0433 report was submitted in 21 December 2017, and the final GS-EU-174-0224 report was submitted 31 May 2018. • Viread has been approved for use in the pediatric HIV infected population 12 to < 18 years of age since 2010, the pediatric HIV infected population 2 to < 12 years of age and the pediatric HBV infected population 12 to < 18 years of age since 2012, and the pediatric HBV infected population 2 to < 12 years of age since 2018. The safety profile of TDF in pediatrics is monitored through routine pharmacovigilance activities and reported in the Viread PSURs/PBRERs, with no new safety concerns identified. • There has not been any evidence to support an increase in the frequency or severity of renal adverse events in pediatrics reported for TDF in the EU since the approval in the HIV and HBV pediatric populations. • Long-term data in both HIV and HBV infected pediatric populations are available up to Week 336 (HIV) and Week 192 (HBV). No new safety concerns were identified from these long-term data. There are no further studies ongoing within the pediatric population. • Renal messages are included in the European treatment guidelines for HIV infection and HBV infection {European AIDS Clinical Society (EACS) 2017}, {European Association for the Study of the Liver (EASL) 2017} {Bamford 2015} and the renal monitoring recommendations are provided in the EU SmPCs for Viread. Given that renal toxicity risk minimization measures in both pediatrics and adults have become fully integrated into standard clinical practice (through inclusion in treatment guidelines), the risk is considered to be fully characterized and appropriately managed. Taking these points together, and given the well-known safety profile of TDF, the MAH considers that the renal safety concerns in HIV-1 and HBV infected pediatric patients can be managed through routine risk minimization activities.

V.3. Summary of Risk Minimization Measures

Viread has the legal status of medicinal product subject to restricted medical prescription in the EU, whereby therapy should be initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B [SmPC section 4.2]). This routine risk minimization measure beyond the product information can be considered a general measure applicable to all of the safety concerns summarized below.

Table Part V.3. 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 Viread (Tenofovir Disoproxil Fumarate)

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

Viread's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Viread should be used.

This summary of the RMP for Viread 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 Viread's RMP.

II. The Medicine and What is it Used for

Viread is authorized for the treatment of patients aged 2 years and above infected with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). Viread is used in combination with other HIV medicines. In children and adolescents its use is only for those who cannot be treated with other first-line nucleos(t)ide reverse transcriptase inhibitors (NRTI) (see Viread SmPC for the full indication).

Viread is also used to treat chronic (long-term) hepatitis B virus (HBV) infection in patients aged 2 years and above with liver damage whose liver is still working properly (compensated liver disease). In adults, it can also be used for those patients with liver damage whose liver is not working properly (decompensated liver disease) and those patients who do not respond to treatment with lamivudine (another medicine used for the treatment of chronic HBV infection) (see Viread SmPC for the full indication).

Viread contains tenofovir disoproxil fumarate (TDF) as the active substance and it is given orally.

Further information about the evaluation of Viread's benefits can be found in Viread'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/viread

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

Important risks of Viread, together with measures to minimize such risks and the proposed studies for learning more about Viread'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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Viread, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (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 Viread is not yet available, it is listed under 'missing information' below.

III.A. List of important risks and missing information

Important risks of Viread are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 Viread. 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

Viread has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby Viread therapy should be initiated by a doctor experienced in the management of HIV infection and/or treatment of chronic hepatitis B (as described in section 4.2 of the SmPC).

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	None
Important Identified Risk	None
Missing Information	None

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 Viread.

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

There are no other studies required for Viread.

PART VII: ANNEXES

Table of Contents

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

None

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

None

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

Not applicable

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

- Referenced material

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

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