



RISK MANAGEMENT PLAN

For

Tenofovir Disoproxil

Version 7.0

RMP Version to be Assessed as Part of this Application:

RMP Version Number	7.0
Data Lock Point for this RMP	18-Nov-2025
Date of Final Sign Off	13-Apr-2026
Rationale for Submitting an Updated RMP	RMP update in line with reference product Viread RMP v27.0, DLP 08-May-2025, date of final sign off: 28-Oct-2025 published by the EMA on 18-Nov-2025
Summary of Significant Changes in this RMP	The following significant changes were made in the current RMP: The RMP has been updated in Part II, III, V, VI and VII Annex 3 and removing all safety concerns, all TFUs, and the additional pharmacovigilance activity (participation in the Antiretroviral Pregnancy Registry).

Other RMP Versions Under Evaluation:

RMP Version Number	Not applicable
Submitted On	Not applicable
Procedure Number	Not applicable

Details of the Current RMP:

Version Number	6.0
Approved with Procedure	Centralized procedure- EMEA/H/C/004049
Date of Approval (Opinion Date)	21-Jul-2022

QPPV name: Andrea Oliva, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
DCP	Decentralised Procedure
DDD	Daily Defined Dose
DHPC	Direct Healthcare Professional Communication
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MRP	Mutual Recognition Procedure
PAC	Patient Alert Card
PL	Package Leaflet
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTC	Patient Treatment Course
PTD	Patient Treatment Days
PTM	Patient Treatment Months
PTY	Patient Treatment Years
PVA	Pharmacovigilance Agreement
QPPV	Qualified Person for Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Activities
DLP	Data Lock Point
SmPC	Summary of Product Characteristics
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Tenofovir disoproxil
Pharmacotherapeutic Group(s) (ATC Code)	Antiviral for systemic use; Nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF07
Marketing Authorisation Holder	Viartis Limited
Medicinal Products to Which this RMP Refers	01
Invented Name(s) in the European Economic Area (EEA)/UK	Tenofovir disoproxil Viartis 245 mg film-coated tablets
Marketing Authorisation Procedure	Centralized procedure- EMEA/H/C/004049
Brief Description of the Product	Chemical class: Antiviral for systemic use; Nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF07 Summary of mode of action: Tenofovir disoproxil maleate is the maleate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells. Tenofovir diphosphate inhibits human immunodeficiency virus (HIV)-1 reverse transcriptase and the hepatitis B virus (HBV) polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into deoxyribonucleic acid (DNA), by DNA chain termination.
Hyperlink to the Product Information:	PI available in module 1.3.1 of the dossier
Indications in the EEA	Current: <u>HIV-1 infection</u> Tenofovir disoproxil 245 mg film-coated tablets are indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults.

	In adults, the demonstration of the benefit of Tenofovir disoproxil in HIV-1 infection is based on results of one study in treatment-naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which tenofovir disoproxil was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml). Tenofovir disoproxil 245 mg film-coated tablets are also indicated for the treatment of HIV-1 infected adolescents, with nucleoside reverse transcriptase inhibitors (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years. The choice of tenofovir disoproxil to treat antiretroviral-experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or treatment history of patients. <u>Hepatitis B infection</u> Tenofovir disoproxil 245 mg film-coated tablets are indicated for the 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 Tenofovir disoproxil 245 mg film-coated tablets are indicated for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age with: • compensated liver disease and evidence of immune active disease, i.e. active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. Proposed: Not applicable
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Dosage in the EEA	Current: Therapy should be initiated by a physician experienced in the management of HIV infection and/or treatment of chronic hepatitis B. <u>Posology</u> <i>Adults</i> The recommended dose of tenofovir disoproxil for the treatment of HIV or for the treatment of chronic hepatitis B is 245 mg (one tablet) once daily taken orally with food. <u>Method of administration</u> Tenofovir disoproxil tablets should be taken once daily, orally with food. However, in exceptional circumstances tenofovir disoproxil 245 mg film-coated tablets can be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice. Proposed: Not applicable
Pharmaceutical Form(s) and Strengths	Current: Film-coated tablets – 250 mg Proposed: Not applicable
Is the Product 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)

Not applicable.

Part II: Module SII - Non-clinical Part of the Safety Specification

Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Not applicable.

Part II: Module SIV - Populations Not Studied in Clinical Trials

Part II: Module SV - Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

The MAH is marketing Tenofovir disoproxil in Australia, Burkina Faso, Burundi, Bolivia, Bahamas, Botswana, Canada, Congo, Côte d'Ivoire, Cameroon, EMA, Ethiopia, Georgia, Ghana, Guatemala, Honduras, Haiti, Indonesia, India, Jamaica, Lao PDR, Lesotho, Mongolia, Malawi, Malaysia, Namibia, Nigeria, Rwanda, Senegal, Swaziland, Chad, Thailand, Trinidad and Tobago, Tanzania, Uganda, South Africa, Zambia and Zimbabwe. The patient exposure has been estimated based on the available cumulative sales data for Tenofovir disoproxil. This data is gathered worldwide from Viatrix Inc.

These figures are compiled from data available at the time of writing and may not represent exact patient consumption. They may include packs that are lodged with wholesalers, pharmacists or representatives. Post-marketing data by indication, age group or by gender is not available.

The calculations for Tenofovir disoproxil have been done based on the WHO Defined Daily Dose (DDD) for tenofovir which is 245 mg.

The methodology used for calculating an estimate of patient exposure for tenofovir is:

$$\text{Patient Treatment Years (PTY)} = \frac{\text{Total mg sold}}{\text{WHO DDD} \times 365}$$

SV.1.2 Exposure

The total worldwide exposure to Tenofovir disoproxil since first market launch, in terms of PTY is estimated to be 1,289,378 patient treatment years.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Not applicable.

Part II: Module SVII - Identified and Potential Risks

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

The MAH has an RMP (v6.0, approved on 21-Jul-2022) for tenofovir disoproxil generic medicine for procedure EMEA/H/C/004049.

Table 2: SVII- Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	• Renal toxicity • Bone events due to proximal renal tubulopathy/loss of bone mineral density
Important Potential Risks	• None
Missing Information	• Safety in pregnancy and lactation • Safety in patients with renal impairment

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

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

The MAH is proposing to remove all safety concerns in its RMP in line with reference product Viread RMP v27.0, DLP 08-May-2025, date of final sign off: 28-Oct-2025 published by the EMA on 18-Nov-2025.

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

Not applicable as this RMP for Tenofovir disoproxil follows the same safety concerns as the reference product RMP (Viread EPAR – Risk management plan summary, published on 18-Nov-2025).

SVII.3.2. Presentation of the Missing Information

Not applicable as this RMP for Tenofovir disoproxil follows the same safety concerns as the reference product RMP (Viread EPAR – Risk management plan summary, published on 18-Nov-2025).

Part II: Module SVIII - Summary of the Safety Concerns

Table 3: SVIII- Summary of safety concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The Pharmacovigilance System Master File contains details of the system and processes that the MAH has in place to identify and characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities only. The Marketing Authorization Holder has in place a routine pharmacovigilance system that will ensure compliance with regulatory agencies for pharmacovigilance responsibilities and will be sufficient to address and monitor the safety profile of Tenofovir. Routine practices are in accordance with standards set by health authorities and the procedures are written to meet the expectations of the health authority.

In line with reference product Viread RMP v27.0, DLP 08-May-2025, date of final sign off: 28-Oct-2025 published by the EMA on 18-Nov-2025, which states “In the PRAC assessment report for the PSUR/PBRER (EMA/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”, the MAH is proposing to remove the specific adverse reaction follow-up questionnaires from its RMP as well.

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

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

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product (Viread, by Gilead).

V.1 Routine Risk Minimisation Measures

Not applicable.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk minimisation measures

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Tenofovir Disoproxil Viatris (Tenofovir disoproxil)

This is a summary of the risk management plan (RMP) for Tenofovir Disoproxil Viatris 245 mg. The RMP details important risks of Tenofovir disoproxil, how these risks can be minimised, and how more information will be obtained about tenofovir's risks and uncertainties (missing information).

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

This summary of the RMP for Tenofovir Disoproxil Viatris should be read in the context of all the 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 Tenofovir Disoproxil Viatris 's RMP.

I. The Medicine and What it is Used For

Tenofovir Disoproxil Viatris 245 mg is authorised for HIV-1 infection in combination with other antiretroviral medicinal products, is also indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years. Tenofovir disoproxil 245 mg film-coated tablets are indicated for the 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 and indicated in treatment of chronic hepatitis B in adolescents 12 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. It contains tenofovir disoproxil as the active substance and it is given by oral route of administration.

Further information about the evaluation of Tenofovir Disoproxil Viatris 245 mg's benefits can be found in Tenofovir Disoproxil Viatris 245 mg's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's [webpage](#).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Tenofovir Disoproxil Viatris 245 mg, together with measures to minimise such risks and the proposed studies for learning more about Tenofovir Disoproxil Viatris 245 mg 's risks, are outlined below.

Measures to minimise 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 authorised 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 minimise its risks.

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Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, 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 Tenofovir Disoproxil Viatri 245 mg is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Tenofovir Disoproxil Viatri 245 mg are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. 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 Tenofovir Disoproxil Viatri 245 mg. 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/use in special patient populations etc.);

Table 4: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tenofovir Disoproxil Viatri 245 mg.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies which are conditions of the marketing authorisation or specific obligation of Tenofovir Disoproxil Viatri 245 mg.