



EU-RISK MANAGEMENT PLAN

For

Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viatriis
(Emtricitabine/Rilpivirine/Tenofovir alafenamide)
Version 0.3

RMP Version to be Assessed as Part of this Application:

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Data Lock Point for this RMP	07-May-2024
Date of Final Sign Off	09-May-2025
Rationale for Submitting an Updated RMP	RMP amended in line with Day 120 list of questions, Rapporteurs Day 150 and Day 173 joint CHMP and PRAC response assessment report dated 25-Mar-2025 and 16-Apr-2025 respectively for Emtricitabine/Rilpivirine/Tenofovir Alafenamide, procedure number EMEA/H/C/006491.
Summary of Significant Changes in this RMP	Minor amendment made to RMP section on first page 'Other RMP Versions Under Evaluation': updated to 'Not applicable'.

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	Not applicable
Approved with Procedure	Not applicable
Date of Approval (Opinion Date)	Not applicable

Approver	Dr. Eiko Soehlke, MD MPH, EEA QPPV
Signature	The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical Classification System
EEA	European Economic Area
EU	European Union
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PL	Package Leaflet
POM	Prescription Only Medicine
PSUR	Periodic Safety Update Report
RT	Reverse Transcriptase
QPPV	Qualified Person for Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Activities
DLP	Data Lock Point
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Emtricitabine/Rilpivirine/Tenofovir Alafenamide
Pharmacotherapeutic Group(s) (ATC Code)	Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC Code: J05AR19
Marketing Authorisation Applicant	Viartis Limited
Medicinal Products to Which this RMP Refers	01
Invented Name(s) in the European Economic Area (EEA)/UK	Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis 200 mg/25 mg/25 mg film-coated tablets
Marketing Authorisation Procedure	Centralised (EMA/H/C/006491)
Brief Description of the Product	<u>Chemical class</u> Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and analogue of 2'-deoxycytidine. Rilpivirine is a diarylpyrimidine NRTI of HIV-1. Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). <u>Mechanism of action</u> Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate competitively inhibits HIV-1 reverse transcriptase (RT), resulting in deoxyribonucleic acid (DNA) chain termination. Emtricitabine has activity against HIV-1, HIV-2, and HBV. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 RT. Rilpivirine does not inhibit the human cellular DNA polymerases α, β and mitochondrial DNA polymerase γ. Due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in loading tenofovir into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV RT, resulting in DNA chain termination. Tenofovir has activity against HIV-1, HIV-2 and HBV. <u>Important information about its composition:</u> Not Applicable

Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier
Indication(s) in the EEA	<u>Current:</u> Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load $\leq 100\,000$ HIV-1 RNA copies/mL. <u>Proposed:</u> Not Applicable
Dosage in the EEA	<u>Current:</u> Therapy should be initiated by a physician experienced in the management of HIV infection. <u>Posology</u> One tablet to be taken once daily with food. If the patient misses a dose of Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis within 12 hours of the time it is usually taken, the patient should take Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule. If the patient vomits within 4 hours of taking Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis another tablet should be taken with food. If a patient vomits more than 4 hours after taking Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis they do not need to take another dose of this medicinal product until the next regularly scheduled dose. <u>Proposed:</u> Not Applicable
Pharmaceutical Form(s) and Strengths	<u>Current:</u> Each film-coated tablet contains 200 mg of emtricitabine, rilpivirine hydrochloride equivalent to 25 mg of rilpivirine and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide.

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	<u>Proposed:</u> Not Applicable
Is/Will 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

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Not applicable.

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

Not applicable.

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

Not applicable.

Part II: Module SV - Post-authorisation Experience

Not applicable.

Part II: Module SVI - Additional EU/UK 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

This is a MAA for a generic medicine which the safety concerns available in the RMP for the reference medicinal product (Odefsey® EPAR RMP Summary dated 21-Jan-2021 published on EMA website)¹ have been adopted by the Applicant.

Table 2: SVII- Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	• None

Summary of Safety Concerns	
Important Potential Risks	• None
Missing Information	• Long-term safety information in adolescents • Safety in pregnancy and lactation

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

Not applicable as all risks from reference product RMP have been considered in this RMP.

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

Not applicable as all risks from reference product RMP have been considered in this RMP.

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

Not applicable as this is the initial RMP for Emtricitabine/Rilpivirine/Tenofovir Alafenamide.

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 Emtricitabine/Rilpivirine/Tenofovir Alafenamide follows the same safety concerns as the safety concerns of the reference substance RMP.

SVII.3.2. Presentation of the Missing Information

Not applicable as this RMP for Emtricitabine/Rilpivirine/Tenofovir Alafenamide follows the same safety concerns as the safety concerns of the reference substance RMP.

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	• Long-term safety information in adolescents • Safety in Pregnancy and Lactation

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

III.1 Routine Pharmacovigilance Activities

There are no other routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

III.2 Additional Pharmacovigilance Activities

The following additional PhV activity is in place for the missing information ‘Safety in Pregnancy and Lactation’

- Participation in the Antiretroviral Pregnancy Registry

Table 4: Part III.1- Antiretroviral Pregnancy Registry Summary

Study Title	The Antiretroviral Pregnancy Registry
Category	3
Rationale and Study Objectives	The purpose of the Antiretroviral Pregnancy Registry is to detect major teratogenic effects of any of the Registry drugs when administered to pregnant women. The combination of increased numbers of HIV-infected pregnant women and the lack of fetal safety data concerning these drugs used during pregnancy, make such a registry an essential component of the ongoing program of epidemiologic studies of the safety of these medications. The objectives of the Antiretroviral Pregnancy Registry are as follows: - To prospectively collect data concerning 1. exposure to the Registry drugs during pregnancy, 2. potential confounding factors, and 3. outcome of pregnancy - To review reported cases of possible birth defects - To estimate the risk of birth defects occurring in live-born offspring of women exposed to antiretroviral medications followed in the Registry during pregnancy - To detect any increase in the prevalence or pattern of birth defects among pregnancies exposed to antiretroviral medications followed in this Registry
Study Design	This is a prospective, observational, exposure-registration, and follow-up study of pregnant patients exposed to antiretroviral drugs. Health care providers voluntarily report exposures to Registry drugs. To assure participant confidentiality, no direct patient identifiers are collected. The intent of the Registry is to collect data on exposures to Registry drugs used alone or in combination, along with potential confounding factors (such as maternal age, clinical category, disease severity), and information related to the outcome of the pregnancy. The Registry

	encourages enrolment as early in the pregnancy as possible before any prenatal testing results are known.
Study Populations	In this voluntary Registry, the population of women eligible for enrolment is pregnant women exposed to one or more of the drugs manufactured or licensed by the Sponsors of the Registry. New sponsors may choose to participate in the Registry as new drugs are approved.
Milestones	Semi-annual reports
	Final report/registry closure: Not applicable In an environment where more antiviral therapies are continually being approved for treatment of HIV, the need for the conjoined Registry continues. However, this Registry could consider discontinuation at such time as the rate of additional approvals for antiretroviral therapies decreases and 1000 first trimester exposures to each antiretroviral therapy is attained or when a subsequent mechanism for monitoring pregnancy outcomes emerges (e.g., standardized national monitoring program).

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 5: Part III.2- On-going and planned additional pharmacovigilance activities

Study & Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required Additional Pharmacovigilance Activities				
Antiretroviral Pregnancy Registry On-going	To collect information on the risk of birth defects in patients exposed to Emtricitabine/Rilpivirine /Tenofovir Alafenamide during pregnancy	- Missing information: Safety in pregnancy	Interim reports	Semi-annual
			Final Report	When 1000 first trimester exposures to each antiretroviral therapy is attained or when a subsequent mechanism for monitoring pregnancy outcomes emerges (e.g., standardized national monitoring program).

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product (Odefsey[®], by Gilead Sciences, Ireland UC).

V.1 Routine Risk Minimisation Measures

Table 6: Part V.1- Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Missing information: Long-term safety information in adolescents	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: Medicine's legal status: POM
Missing information: Safety in pregnancy and lactation	Routine risk communication: SmPC section 4.6 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: Medicine's legal status: POM

V.2 Additional Risk Minimisation Measures

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

V.3 Summary of Risk minimisation measures

Table 7: Part V.3- Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing information: Long-term safety information in adolescents	Routine risk minimization measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

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Missing information: Safety in Pregnancy and Lactation	Routine risk minimization measures: SmPC section 4.6 PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry (APR)
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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis (Emtricitabine/Rilpivirine/Tenofovir Alafenamide)

This is a summary of the risk management plan (RMP) for Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis. The RMP details important risks of Emtricitabine/Rilpivirine/Tenofovir Alafenamide how these risks can be minimised, and how more information will be obtained about Emtricitabine/Rilpivirine/Tenofovir Alafenamide 's risks and uncertainties (missing information).

Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis'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 Emtricitabine/Rilpivirine/Tenofovir alafenamide Viartis 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 Emtricitabine/Rilpivirine /Tenofovir alafenamide Viartis's RMP.

I. The Medicine and What it is Used For

Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load $\leq 100\,000$ HIV 1 RNA copies/mL. (see SmPC for the full indication).

It contains Emtricitabine/Rilpivirine/Tenofovir Alafenamide as the active substance and it is given orally.

Further information about the evaluation of Emtricitabine/Rilpivirine/Tenofovir alafenamide Viartis's benefits can be found in Emtricitabine/Rilpivirine/Tenofovir alafenamide Viartis'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 Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis together with measures to minimise such 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 minimises 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 Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis 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 Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis. 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 8: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• None
Important Potential Risks	• None
Missing Information	• Long-term safety information in adolescents • Safety in Pregnancy and Lactation

II.B Summary of Important Risks

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

Table 9: Part VI.2- Missing Information: Long-term safety information in adolescents

Risk Measures	Minimisation Routine risk minimisation measures None Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern
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Table 10: Part VI.3- Missing Information: Safety in pregnancy and lactation

Risk Measures	Minimisation Routine risk minimisation measures SmPC Section 4.6 PL Section 2 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern
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Additional Pharmacovigilance Activities	Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry. See section II.C of this summary for an overview of the post-authorisation development plan.
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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 Emtricitabine/Rilpivirine/Tenofovir Alafenamide Viartis.

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

Antiretroviral Pregnancy Registry.

Purpose of the study:

To collect information on the risk of birth defects in patients exposed to antiretroviral drugs (ARVs), including Emtricitabine/Rilpivirine/Tenofovir alafenamide Viartis, during pregnancy.

PART VII: ANNEXES

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable.