EU-RISK MANAGEMENT PLAN
For
Emtricitabine/Tenofovir alafenamide Viatris
(Emtricitabine/Tenofovir alafenamide)
Version 0.3

RMP Version to be Assessed as Part of this Application:

RMP Version Number	0.3
Data Lock Point for this RMP	24-Apr-2024
Date of Final Sign Off	08-Apr-2025
Rationale for Submitting an Updated RMP	RMP amended inline with Rapporteurs Updated Day 150 Joint CHMP and PRAC Response Assessment Report and the list of questions dated 20-Mar-2025.
Summary of Significant Changes in this RMP	Minor update made to Part V (V.1).

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	RMP has been reviewed and approved by the marketing authorisation applicant's QPPV and that the electronic signature is on file.
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LIST OF ABBREVIATIONS

Abbreviation	Definition
APR	Antiretroviral Pregnancy Registry
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
DNA	Deoxyribonucleic acid
DCP	Decentralised Procedure
DDD	Daily Defined Dose
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
HIV-1	Human immunodeficiency virus type 1
HIV-2	Human immunodeficiency virus type 2
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MRP	Mutual Recognition Procedure
NRTI	Nucleoside reverse transcriptase inhibitor
PBMCs	Peripheral blood mononuclear cells
POM	Prescription Only Medicine
PL	Package Leaflet
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
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/Tenofovir alafenamide
Pharmacotherapeutic Group(s) (ATC Code)	Antiviral for systemic use; antivirals for treatment of HIV infections, combinations, ATC code: J05AR17
Marketing Authorisation Applicant	Viatris Limited
Medicinal Products to Which this RMP Refers	1
Invented Name(s) in the European Economic Area (EEA)	Emtricitabine/Tenofovir alafenamide Viatris 200 mg/10 mg film coated tablets Emtricitabine/Tenofovir alafenamide Viatris 200 mg/25 mg film coated tablets
Marketing Authorisation Procedure	Centralised (EMEA/H/C/006469)
Brief Description of the Product	Chemical class Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and nucleoside analogue of 2'-deoxycytidine. Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue) Summary of mode of action Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine triphosphate. Emtricitabine triphosphate inhibits HIV replication through incorporation into viral deoxyribonucleic acid (DNA) by the HIV reverse transcriptase (RT), which results in DNA chain-termination. Emtricitabine has activity against HIV-1, HIV-2, and HBV. Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination. Tenofovir has activity against HIV-1, HIV-2, and HBV. Important information about its composition: Not Applicable

<table>
<tr><td>Hyperlink to the Product Information:</td><td>PI available in section 1.3.1 of the dossier</td></tr>
<tr><td>Indication(s) in the EEA</td><td><u>Current</u>:
Emtricitabine/Tenofovir alafenamide Viatris is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1)

<u>Proposed</u>:
Not Applicable</td></tr>
<tr><td>Dosage in the EEA</td><td><u>Current</u>:
Emtricitabine/Tenofovir alafenamide 200 mg/10 mg, 200 mg/25 mg film coated tablets should be initiated by a physician experienced in the management of HIV infection.

<u>Posology</u>:
Dose of Emtricitabine/Tenofovir alafenamide Viatris according to third agent in the HIV treatment regimen

<table>
<tr><th>Dose of Emtricitabine/Tenofovir alafenamide Viatris</th><th>Third agent in HIV treatment regimen</th></tr>
<tr><td>Emtricitabine/Tenofovir alafenamide Viatris 200/10 mg once daily</td><td>Atazanavir with ritonavir or cobicistat
Darunavir with ritonavir or cobicistat[1]
Lopinavir with ritonavir</td></tr>
<tr><td>Emtricitabine/Tenofovir alafenamide Viatris 200/25 mg once daily</td><td>Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir</td></tr>
</table>
[1] Emtricitabine/Tenofovir alafenamide 200/10 mg in combination with darunavir 800 mg and cobicistat 150 mg, administered as a fixed-dose combination tablet, was studied in treatment-naive subjects, see section 5.1.

Method of administration:
Emtricitabine/Tenofovir alafenamide Viatris should be taken once daily with or without food. It is recommended that the film-coated tablet is not chewed or crushed due to the bitter taste.

For patients who are unable to swallow the tablet whole, the tablet may be split in half and both halves taken one after the other, ensuring that the full dose is taken immediately.

<u>Proposed</u>:
Not Applicable</td></tr>
</table>

Pharmaceutical Form(s) and Strengths	Current: 200 mg/10 mg film coated tablets Each tablet contains 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 10 mg of tenofovir alafenamide. 200 mg/25 mg film coated tablets Each tablet contains 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 25 mg of tenofovir alafenamide 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)

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

Not applicable.

Part II: Module SV - Post-authorisation Experience

Not applicable

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

This is a MAA for a generic medicine in which the safety concerns available in the RMP for the reference medicinal product (Descovy® EPAR RMP Summary dated 14-Nov-2022) [1] have been adopted by the MAH.

Table 2: SVII- Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	None
Missing Information	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/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/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/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: SVII- Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	None
Missing Information	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:

• 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/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 (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 (Descovy® 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: 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: Not applicable. **Other routine risk minimisation measures beyond the Product Information** Medicine's legal status: Prescription only medicine (POM)

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

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: 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)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Emtricitabine/Tenofovir alafenamide Viatris (Emtricitabine/Tenofovir alafenamide)

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

Emtricitabine/Tenofovir alafenamide 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 Emtricitabine/Tenofovir alafenamide 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 Emtricitabine/Tenofovir alafenamide Viatris's RMP.

I. The Medicine and What it is Used For

Emtricitabine/Tenofovir alafenamide Viatris is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1) (see SmPC for the full indication). It contains Emtricitabine/Tenofovir alafenamide as the active substance and it is given by oral route of administration.

Further information about the evaluation of Emtricitabine/Tenofovir alafenamide Viatris’s benefits can be found in Emtricitabine/Tenofovir alafenamide Viatris’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/Tenofovir alafenamide Viatris, together with measures to minimise such risks and the proposed studies for learning more about Emtricitabine/Tenofovir alafenamide Viatris'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 minimises its risks.

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/Tenofovir alafenamide Viatris is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Emtricitabine/Tenofovir alafenamide Viatris are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely 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/Tenofovir alafenamide Viatris. 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	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.4- Missing Information: Safety in pregnancy and lactation

Risk Minimisation Measures	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
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.

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/Tenofovir alafenamide Viatris.

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/Tenofovir alafenamide Viatris 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.