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

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

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

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

I. The Medicine and What is it Used for

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

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

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

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

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

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

Together, these measures constitute routine risk minimization measures.

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

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

II.A. List of important risks and missing information

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

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

Important Identified Risks	Renal toxicity (TDF)
	Bone events due to proximal renal tubulopathy/loss of bone mineral density (TDF)
Important Potential Risks	None
Missing Information	Safety in pregnancy and lactation (RPV, TDF)
	Safety in patients with renal impairment (TDF)

II.B. Summary of Important Risks

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

Table Part V1.2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	**Renal Toxicity (TDF)**
Evidence for linking the risk to the medicine	Renal failure, renal impairment, elevated creatinine, hypophosphatemia and PRT (including Fanconi syndrome) have been reported with the use of TDF in clinical trials and postmarketing setting.
Risk factors and risk groups	Risk factors for renal events include advanced HIV disease (low CD4 count at the start of treatment), low weight, older age, renal impairment before starting therapy, use of other medicines that are damaging to kidneys, high blood pressure, and also being infected with hepatitis C.
Risk Minimization Measure(s)	Routine risk communication: SmPC Sections: 4.2, 4.3, 4.4, 4.5, and 4.8 PL Sections: 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Sections: 4.4: Recommendation for renal function monitoring and guidance on when to interrupt or discontinue EPA Additional risk minimization measures: No risk minimization measures.
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Monitoring reversibility of renal parameters in patients who discontinue TDF due to renal tubulopathy in clinical studies of TDF-containing products See Section II.C of this summary for an overview of the post-authorization development plan.
Important Identified Risk	**Bone Events Due to Proximal Renal Tubulopathy/Loss of Bone Mineral Density (TDF)**
Evidence for linking the risk to the medicine	Clinical trial data indicate that decreases in BMD observed following the initiation of ART appear to be greater with regimens containing TDF compared to those without TDF. Analysis of postmarketing spontaneous AE reports has indicated that there may be rare occurrences of osteomalacia (manifested as bone pain and infrequently contributing to fractures) as a consequence of PRT in patients treated with TDF.
Risk factors and risk groups	HIV infection is known to be associated with bone disease.
Risk Minimization Measure(s)	Routine risk communication: SmPC Sections: 4.4 and 4.8 PL Sections: 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section: 4.4: Guidance on action to be taken if bone abnormalities are suspected Additional risk minimization measures: No risk minimization measures.
Additional Pharmacovigilance activities	None
Missing information	**Safety in Pregnancy and Lactation (RPV, TDF)**

Risk Minimization Measure(s)	Routine risk communication: SmPC Section: 4.6 PL Section: 2 Additional risk minimization measures: SmPC Sections: 4.2, 4.4, 4.8 PL Section: 2
Additional Pharmacovigilance activities	Antiretroviral Pregnancy Registry See Section II.C of this summary for an overview of the post-authorization development plan.
Missing information	**Safety in patients with renal impairment (TDF)**
Risk Minimization Measure(s)	Routine risk communication: SmPC Sections: 4.2, 4.4, 4.8 PL Section: 2 Additional risk minimization measures: No risk minimization measures.
Additional Pharmacovigilance activities	None

II.C. Post-authorization Development Plan

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

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

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

Table Part V1.3. Other Studies in Post-Authorization Development Plan

Short Study Name	Purpose of the Study
Antiretroviral Pregnancy Registry	*Objectives:* To collect information on the risk of birth defects in patients exposed to anti-HIV medicines, including the components of Eviplera, during pregnancy *Safety concern(s) addressed:* Missing information: Safety in pregnancy and lactation
Monitoring of reversibility of renal tubulopathy in clinical trials	*Objectives:* To collect information on the reversibility of renal tubulopathy following stopping treatment with TDF in adult patients and children *Safety concern(s) addressed:* Important identified risk: Renal toxicity