SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Tenofovir Disoproxil Mylan 245 mg (Tenofovir Disoproxil)

This is a summary of the risk management plan (RMP) for Tenofovir Disoproxil Mylan 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 Mylan 245 mg'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 Mylan 245 mg 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 Mylan 245 mg's RMP.

The medicine and what it is used for

Tenofovir Disoproxil Mylan 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 Mylan 245 mg's benefits can be found in Tenofovir Disoproxil Mylan 245 mg's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage[1].

Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

[1] https://www.ema.europa.eu/en/medicines/human/EPAR/tenofovir-disoproxil-mylan

- 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 Tenofovir Disoproxil Mylan 245 mg is not yet available, it is listed under 'missing information' below.

List of important risks and missing information

Important risks of Tenofovir Disoproxil Mylan 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 Mylan 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.).

Summary of safety concerns

List of important risks and missing information	
Important identified risks	• Kidney problems (Renal toxicity) • Reduction in bone density and bone problems due to kidney disease (Bone events due to proximal renal tubulopathy/loss of bone mineral density)
Important potential risks	• None
Missing information	• Limited safety information on use during pregnancy and breast-feeding • Limited safety information on use in patients with kidney impairment

Summary of important risks

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

Important identified risks	**Kidney problems (Renal toxicity)**
Evidence for linking the risk to the medicine	Renal failure, renal impairment, elevated creatinine in blood, low levels of phosphate in blood (hypophosphatemia) and damage to kidney tubule cells (proximal renal tubulopathy [including Fanconi syndrome]) have been reported with the use of tenofovir disoproxil fumarate (TDF) in clinical trials and in the 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 virus.
Risk minimization measure(s)	Routine risk communication: SmPC sections 4.2, 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 section 4.4: Recommendation for renal function monitoring and guidance on when to interrupt or discontinue TDF. SmPC section 4.4: Guidance that, for pediatric patients, a multidisciplinary approach is recommended to adequately weigh the benefit/risk balance of treatment, decide the appropriate monitoring and consider the need for supplementation
Important identified risks	**Reduction in bone density and bone problems due to kidney disease (Bone events due to proximal renal tubulopathy/loss of bone mineral density)**
Evidence for linking the risk to the medicine	In the postmarketing setting, there have been rare occurrences of damage to kidney tubule cells associated with TDF therapy leading to bone softening (osteomalacia) with bone pain and sometimes resulting in fractures. Thinning of bones (decreases in bone mineral density [BMD]) has been observed in patients treated with TDF during clinical trials. However, the clinical significance is unknown as no increase in fracture rates has been observed.

Risk factors and risk groups	HIV infection is known to be associated with bone disease. Reduced BMD and impaired calcium metabolism is known to be associated with cirrhosis of the liver. A number of small studies have shown that people with liver cirrhosis related to hepatitis B or hepatitis C virus infection have reduced BMD and reductions in BMD are correlated with the severity of liver disease.
Risk minimization measure(s)	Routine risk communication: SmPC sections 4.4, 4.8 and 5.1 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 SmPC section 4.4: Guidance that, for pediatric patients, a multidisciplinary approach is recommended to adequately weigh the benefit/risk balance of treatment, decide the appropriate monitoring and consider the need for supplementation
Missing information	**Limited safety information on use during pregnancy and breast-feeding**
Risk minimization measure(s)	Routine risk communication: SmPC sections 4.6 and 5.3 PL section 2
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry
Missing information	**Limited safety information on use in patients with kidney impairment**
Risk minimization measure(s)	Routine risk communication: SmPC sections 4.2, 4.4, 4.8 and 5.2 PL sections 2 Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC section 4.4: Recommendation for dosage adjustment and close monitoring of renal function if TDF is used in an adult patient with creatinine clearance < 50 ml/min. The use of TDF is not recommended in pediatric patients with renal impairment.

Post-authorisation development plan

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 Mylan 245 mg.

Other studies in post-authorisation development plan

Antiretroviral Pregnancy Registry.

Purpose of study: To collect information on the risk of birth defects in patients exposed to tenofovir during pregnancy.