VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Human immunodeficiency virus (HIV)
HIV is a type of virus that attacks the body's natural defense system. AIDS refers to a range of infections/illnesses due to weakened immune system. HIV is of two types, HIV-1 (found worldwide) and HIV-2 (generally confined to West Africa). HIV is passed through sexual contact (most common), infected blood transfusions, needle sharing and to an unborn baby through HIV-positive mother. In 2013, 136,235 new HIV diagnoses were reported in 51 of the 53 countries of the WHO European Region and 29,157 HIV diagnoses were reported by 30 European Union / European Economic Area (EU/EEA) countries, with a rate of 5.7/100,000 population. The overall rate for men and women in the EU/EEA were 8.9 and 2.6 per 100,000 population, respectively. Highest rates (per 100,000 population) of HIV diagnoses were in Estonia (24.6) and Latvia (16.8), and lowest rates were in Slovakia (1.5) and Croatia (2.0). Less than 1% of HIV-infected people died in 2013.

Hepatitis B
Hepatitis B infection is one of the world's most common and serious infectious diseases. It is a potentially life-threatening infection caused by hepatitis B virus (HBV) that attacks liver and can cause both acute (short-term) and chronic (long-term) disease. About 5% of the population are chronic carriers of HBV. Nearly 25% of all carriers develop serious liver diseases and liver cancer. HBV infection causes more than one million deaths every year.

People with HBV infection often do not have any symptoms; therefore, individuals may not be aware that they have been infected, although they are still able to infect others. People who are more at risk of developing infections caused by HBV include people having unprotected sexual contact or sharing needles with an infected person, visiting endemic regions, frequently receiving blood/blood products, occupations involving contact with blood, household contacts of HBV carriers and mother-to-baby transmission.

VI.2.2 Summary of treatment benefits

Tenofovir is a type of anti-viral medicine (nucleoside and nucleotide reverse transcriptase inhibitors). It acts by interfering with the normal functioning of certain enzymes of HIV and HBV that are essential for virus reproduction thereby reducing the amount of viruses in the body and keeping it at a low level. This medicine is not a cure of HIV or HBV infection.

Tenofovir is used in combination with at least one other antiviral medicine to treat adults who are infected with HIV and in adolescents (12 to <18 years), and adults for the treatment of chronic HBV. It should be noted that while taking Tenofovir, the patient may still develop other illness or infection associated with the disease.

A long-term study (144-weeks) evaluated the effectiveness (efficacy) and safety of tenofovir disoproxil 245 mg versus other types of antiretrovirals (stavudine when used in combination with lamivudine and efavirenz) in treatment-naïve HIV-1 infected adult patients. At baseline, nearly half (43%) of the patients had high number of virus in blood (>100,000 copies/mL) and more than one-third of the patients (39%) had low immune defense mechanism (CD4 cell counts <200 cells/mL). At 144 weeks of treatment, the proportion of patients with reduced viral copies (HIV-1 RNA below 400 copies/mL and 50 copies/mL) were higher in the tenofovir disoproxil 245 mg arm compared to stavudine arm.

VI.2.3 Unknowns relating to treatment benefits

Safety and treatment benefits are unknown in patients over the age of 65 years, children (under the age of 2 years, chronic HBV infection less than 12 years or weighing less than 35 kg), patients with impaired kidney function, use in pregnancy and lactation, black HBV infected patients, HBV patients with severe irreversible liver function according to CPT score (including long-term safety) and liver transplant recipients infected with HBV.

VI.2.4 Summary of safety concerns

VI.2.4.1 Summary of safety concerns for identified risk

Table No: VI.2.4.1

Risk	What is known	Preventability
Post-treatment hepatic flares in HBV mono-infected and HIV/HBV co-infected patients (liver problems on stopping treatment in patients who have only hepatitis B, and patients who have HIV and hepatitis B [a type of liver disorder])	Acute worsening of hepatitis is reported in patients who have discontinued hepatitis B therapy. Post-treatment worsening are usually associated in rising HBV levels, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported in patients with irreparable liver disease.	1. Doctors are advised to closely monitor patients mono-infected with HBV and co-infected with HIV and HBV clinically and laboratory follow-up for at least several months after stopping treatment with Tenofovir.
Renal (kidney) toxicity (harmful effect)	Inflammation of the kidney, passing a lot of urine and feeling thirsty, damage to kidney tubule cells changes to child's urine and back pain caused by kidney problems, including kidney failure are rare side effects of Tenofovir (i.e. can affect up to 1 in every 1,000 patients). Before starting treatment, treating doctor may order blood tests to assess kidney function. The doctor may also order blood tests during treatment to monitor kidney function and may advise to take the tablets less often. Tenofovir is not recommended in case of severe kidney disease or patients who are receiving haemodialysis. Tenofovir is not usually taken with other medicines that can damage kidneys. If this is unavoidable, the doctor needs to monitor the kidney function regularly.	1. Doctors are advised to regularly monitor renal functions in patients who are susceptible to kidney impairment so as to arrive at an early diagnosis of impaired renal function in patients being treated Tenofovir. 2. Patients with renal impairment may require close monitoring of kidney function (i.e. prior to initiating therapy, after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without kidney risk factors. In patients at risk for kidney impairment, a more frequent monitoring of renal function is required) and dose interval adjustments are recommended for patients with creatinine clearance (a measure of kidney function)

Risk	What is known	Preventability
	The following side-effects are rare (these can affect up to 1 in every 1,000 patients): inflammation of the kidney, passing a lot of urine and feeling thirsty, reduced kidney function, kidney failure, damage to kidney tubule cells.	between 30 and 49 mL/min. 3. Patients are advised to inform their doctors if they have any pre-existing kidney dysfunction.
Bone events due to proximal renal tubulopathy (type of kidney disease)/loss of BMD (decrease in minerals in bones)	Damage to kidney tubule cells may be associated with breakdown of muscle, softening of the bones (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood. Decrease in blood phosphate is a very common side effect (i.e. can affect at least 10 in every 100 patients) whereas decrease in blood potassium is a common side effect (i.e. can affect up to 10 in every 100 patients).	1. In patients receiving Tenofovir, rare events of renal impairment, renal failure and proximal renal tubulopathy (type of kidney disease) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended in such patients. 2. Patients are advised to inform their doctors if they notice any warning symptoms like bone pain.
Drug interaction with an Didanosine (a type of antiviral [anti-HIV] medicine)	Taking Tenofovir with other antiviral medicines that contain Didanosine can raise the levels of Didanosine in blood and may reduce CD4 cell counts (a type of cell). Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes causes death, have been reported when medicines containing Tenofovir disoproxil and Didanosine were taken together. The treating doctor needs to carefully consider whether to treat a patient with combinations of Tenofovir and Didanosine.	1. Patients are advised to immediately inform their doctors about all the medications they are taking prior to starting treatment with Tenofovir.
Pancreatitis (inflammation of pancreas)	About 1 in every 100 patients experienced pain in the tummy caused by inflammation of the pancreas. Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), have caused death. This has been reported when medicines containing Tenofovir disoproxil and Didanosine were taken together.	1. Doctors can avoid co-prescribing Tenofovir with a medication called Didanosine as it is known to cause pancreatitis. 2. Patients are advised to discuss with their doctors prior to starting treatment with Tenofovir.

VI.2.4.2 Summary of safety concerns for potential risks

Table No: VI.2.4.2

Risk	What is known
Development of resistance (ability of micro-organisms to resist the effect of drug) during long-term exposure in HBV infected patients	There have been reports of a high rate of failure of viral reduction in blood and of emergence of resistance at an early stage when tenofovir disoproxil was combined with other anti-retroviral drugs (lamivudine, Abacavir, lamivudine and didanosine) as a once daily regimen. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. Dose of tenofovir should be taken always as recommended by the doctor to ensure the drug is fully effective and reduce the risk of developing resistance to the treatment.

VI.2.4.3 Summary of safety concerns for missing information

Table No: VI.2.4.3

Risk	What is known
Safety in children (including long-term safety)	Tenofovir is not recommended in children under the age of 2 years as the safety and efficacy of Tenofovir have not been established in this population.
Safety in elderly patients	Tenofovir has not been studied in patients over the age of 65 years. Elderly patients are more likely to have decreased renal (kidney) function; therefore caution should be exercised when treating elderly patients with Tenofovir.
Safety in pregnancy	A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicates no malformations or foetal/neonatal toxicity associated with Tenofovir disoproxil. Therefore the use of Tenofovir may be considered during pregnancy, if necessary.
Safety in lactation (during breast-feeding)	Tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of Tenofovir in newborns/infants. Therefore Tenofovir should not be used during breast-feeding. As a general rule, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV to the infant.
Safety in patients with renal impairment	There are limited data on the safety and efficacy of Tenofovir in patients with moderate and severe renal impairment and long-term safety data has not been evaluated for mild renal impairment. Therefore, in patients with renal impairment Tenofovir should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Patients with renal impairment may require close monitoring of renal function. Dose interval adjustments are recommended for patients with creatinine clearance (a measure of kidney function) between 30 and 49 mL/min. These dose adjustments have not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in these patients.

Risk	What is known
Safety in black HBV infected patients	Safety or efficacy data in black HBV infected patients is currently not known.
Safety in HBV infected patients with decompensated liver disease and CPT score >9 (including long-term safety)	Tenofovir pharmacokinetics were not substantially altered in non-HIV subjects with various degrees of hepatic impairment who received a single 245 mg dose Tenofovir. Safety or efficacy data HBV infected patients with severe irreversible liver disease according to CPT classification (including long-term safety) is currently not known.
Safety in liver transplant recipients infected with HBV	Safety or efficacy data in liver transplant recipient patients infected with HBV is currently not known.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the patient information leaflet. The measures in these documents are known as routine risk minimisation measures.

The SmPC and the PIL for Tenofovir film-coated tablets can be found in the Tenofovir EPAR page.

Tenofovir has additional risk minimisation measures. Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in Tenofovir 245 mg Film-coated Tablets's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Renal toxicity
Risk minimisation measures: • Kidney educational program, renal educational brochure including creatinine clearance slide ruler distributed to prescribers. • The educational material will be discussed and agreed with the national competent authority prior to actual launch of the product.
Objective and rationale: • To increase the understanding and awareness of renal toxicity associated with Tenofovir. • To enable doctors arrive at an early diagnosis of renal toxicity in patients being treated with Tenofovir and understand the importance of assessing creatinine clearance at baseline and during therapy.

Summary description of main additional risk minimisation measures: Kidney educational program, renal educational brochure including creatinine clearance slide ruler distributed to prescribers. The educational material will be discussed and agreed with the national competent authority prior to actual launch of the product.
Safety in children (including long-term safety)
Risk minimisation measures: • Educational material (HIV and HBV paediatric educational brochures) distributed to prescribers. • The educational material will be discussed and agreed with the national competent authority prior to actual launch of the product.
Objective and rationale: • To inform doctors that safety and efficacy of Tenofovir has not been established in HIV-1 infected children under 2 years of age and in children with chronic hepatitis B aged 2 to less than 12 years or weighing less than 35 kg.
Summary description of main additional risk minimisation measures: Educational material (HIV and HBV paediatric educational brochures) distributed to prescribers. The educational material will be discussed and agreed with the national competent authority prior to actual launch of the product.
Safety in patients with renal impairment
Risk minimisation measures: • Educational material (HIV and HBV renal educational brochures including creatinine slide ruler) distributed to prescribers. • The educational material will be discussed and agreed with the national competent authority prior to actual launch of the product.
Objective and rationale: • To inform doctors that dosing adjustment is required in all patients with creatinine clearance <50 mL/min. • Doctors are advised to calculate creatinine clearance in all patients prior to initiating therapy and, as clinically appropriate during Tenofovir therapy.
Summary description of main additional risk minimisation measures: Kidney educational program, renal educational brochure including creatinine clearance slide ruler distributed to prescribers. The educational material will be discussed and agreed with the national competent authority prior to actual launch of the product.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time are included in the below table.

Version	Date	Safety Concerns	Comments
1.0	07 December 2015	Important identified Risk: • Post-treatment hepatic flares in HIV-1/HBV co-infected patients • Lactic acidosis and severe hepatomegaly with steatosis • Lipodystrophy • Renal toxicity • Bone events due to proximal renal tubulopathy/loss of bone mineral density (BMD) • Drug interaction with didanosine • Pancreatitis Potential Risks: Nil Missing information: • Safety in children (including long-term safety) • Safety in elderly patients • Safety in pregnancy and lactation • Safety in patients with renal impairment	None
1.1	27 July 2016	Important identified Risk: • Post-treatment hepatic flares in HBV mono-infected and HIV/HBV co-infected patients • Renal toxicity • Bone events due to proximal renal tubulopathy/loss of BMD • Drug interaction with didanosine • Pancreatitis Potential Risks: • Development of resistance during long-term exposure in HBV infected patients Missing information: • Safety in children (including long-term safety) • Safety in elderly patients • Safety in pregnancy • Safety in lactation • Safety in patients with renal impairment • Safety in black HBV infected patients • Safety in HBV infected patients with decompensated liver disease and CPT score >9 (including long-term safety) • Safety in liver transplant recipients infected with HBV	Changes in the safety concerns are done based on assessor's comments in RMS Day 70 Preliminary Assessment Report.

Version	Date	Safety Concerns	Comments
2.0	29-Aug-2016	Important identified Risk: • Post-treatment hepatic flares in HBV mono-infected and HIV/HBV co-infected patients • Renal toxicity • Bone events due to proximal renal tubulopathy/loss of BMD • Drug interaction with didanosine • Pancreatitis Potential Risks: • Development of resistance during long-term exposure in HBV infected patients Missing information: • Safety in children (including long-term safety) • Safety in elderly patients • Safety in pregnancy • Safety in lactation • Safety in patients with renal impairment • Safety in black HBV infected patients • Safety in HBV infected patients with decompensated liver disease and CPT score >9 (including long-term safety) • Safety in liver transplant recipients infected with HBV	RMP aligned with SmPC and PIL updated after assessor's comments in CMS Comments on Day 70 Preliminary Assessment Report.
2.1	25 January 2017	Important identified Risk: • Post-treatment hepatic flares in HBV mono-infected and HIV/HBV co-infected patients • Renal toxicity • Bone events due to proximal renal tubulopathy/loss of BMD • Drug interaction with didanosine • Pancreatitis Potential Risks: • Development of resistance during long-term exposure in HBV infected patients Missing information: • Safety in children (including long-term safety) • Safety in elderly patients • Safety in pregnancy • Safety in lactation • Safety in patients with renal impairment • Safety in black HBV infected patients • Safety in HBV infected patients with decompensated liver disease and CPT score >9 (including long-term safety) • Safety in liver transplant recipients infected with HBV	RMP aligned with minor updates to SmPC