Part VI.2 Elements for a Public Summary

Part VI.2.1 Overview of disease epidemiology

Human immunodeficiency virus (HIV)-1 infection:

HIV that causes acquired immunodeficiency syndrome (AIDS), has become one of the world's most serious health and development challenges. According to United Nations, global occurrence rate was 0.8% in the infected patients of age group between 15-49 years and 1.2 million people died of AIDS in 2014. There were about 2 million new infections in 2015. Women represent approximately half (51%) of all adults living with HIV worldwide and is the leading cause of death among women of reproductive age. 70% of people living with HIV are found in Sub-Saharan Africa with South Africa having the highest number of people living with HIV in the world (6.8 million). About 2 million people in Latin America and the Caribbean combined, 1.5 million people in Eastern Europe & Central Asia and 5 million people in Asia and the Pacific are estimated to be living with HIV [KHJF Foundation, 2015].

Pre-exposure prophylaxis (PrEP):

PrEP with antiretroviral medications has been widely recognized as a method for primary prevention for individuals with ongoing risks for becoming infected with HIV. It gains a central role in prevention of HIV infection amongst men who have sex with men (MSM) and has been vigorously promoted in San Francisco, California, United States of America [Snowden et al., 2017]. More than 29,000 persons were diagnosed with HIV in the 30 countries of the European Union and European Economic Area (EU/EEA) in 2013. The majority of these infections were because of sexual transmission, 12 000 (42%) of the new diagnoses were among MSM, and nearly 10 000 (32%) were among heterosexuals, many from countries with high HIV prevalence [Cairns et al., 2016].

Part VI.2.2 Summary of treatment benefits

Emtricitabine and tenofovir a nucleotide for once-daily oral administration are used in the treatment of adults and adolescents with HIV-1 infection. Emtricitabine and tenofovir was effective in the initial treatment of patients with HIV-1 infection [Perry CM, 2009].

Tenofovir-emtricitabine represents one of the more recent fixed-dose combinations and has significantly lowered (reduced) HIV-related proportion of sickness (morbidity) and deaths (mortality). Additonally fewer side effects, less harmful effects (reduced toxicity), and simplified dosing are being observed [Masho et al., 2007].

Part VI.2.3 Unknowns relating to treatment benefits

The efficacy of emtricitabine/tenofovir disoproxil in children under the age of 12 years and in patients with significant underlying liver disorders has not been established.

Emtricitabine/tenofovir disoproxil has not been studied in patients over the age of 65 years.

Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Sudden worsening of symptoms of hepatitis after discontinuation of treatment with anti HIV drugs which also shows some activity against HBV infection (Post-treatment hepatic flares in HIV-1/HBV co-infected patients)	Patients infected with HIV who also have liver disease (including chronic hepatitis B or C), who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications which are severe and may result in death. Both active substances in emtricitabine/tenofovir disoproxil show some activity against HBV although emtricitabine is not approved for the treatment of hepatitis B infection. Discontinuation of emtricitabine/tenofovir disoproxil therapy in patients co-infected with HIV and HBV may cause sudden worsening of hepatitis. Worsened hepatitis after the HIV treatment may lead to life-threatening complications of liver disease and eventually death. Fatty liver, and yellow skin or eyes, itching, or pain in the abdomen (tummy) caused by inflammation of the liver are rare side effects of emtricitabine/tenofovir disoproxil. Tests may also show problems associated with the liver.	If patients have hepatitis B or C infection, the best treatment regimen should be carefully considered by the doctor. If patients have a history of liver disease or chronic hepatitis B (CHB) infection the doctor should conduct blood tests in order to carefully monitor liver function. Patient should know their HBV status before starting the treatment with emtricitabine/tenofovir disoproxil. If the patient is suffering from HBV, there is a serious risk of liver problems after stopping the treatment with emtricitabine/tenofovir disoproxil, whether or not the patient also has HIV. It is important not to stop taking emtricitabine/tenofovir disoproxil, without talking to the doctor first. Patient might require blood tests for several months after stopping treatment. In some patients with advanced liver disease or cirrhosis, (an abnormal liver condition in which there is irreversible scarring of the liver) stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening. Doctor should be immediately informed about new or unusual symptoms after stopping the treatment, particularly symptoms associated with hepatitis B infection.
Harmful effects to kidney caused by use of medicine (Renal toxicity)	A higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease	Emtricitabine/tenofovir disoproxil may affect kidneys so it is not recommended if patients have severe kidney disease or are receiving dialysis (a process of purifying

Risk	What is known	Preventability
	inhibitor (anti HIV medicines) Emtricitabine/tenofovir disoproxil is not usually taken with other medicines that can damage kidneys like aminoglycosides (for bacterial infection), amphotericin B (for fungal infection), foscarnet (for viral infection), ganciclovir (for viral infection), pentamidine (for infections), vancomycin (for bacterial infection), interleukin-2 (to treat cancer), cidofovir (for viral infection) and NSAIDs (to relieve bone or muscle pains). Inflammation of the kidney, passing a lot of urine and feeling thirsty, kidney failure, damage to kidney tubule cells, and back pain caused by kidney problems are rare side effects of emtricitabine/tenofovir disoproxil. Breakdown of muscle, muscle pain or weakness which may occur due to damage to the kidney tubule cells are uncommon side effects of emtricitabine/tenofovir disoproxil. Damage to kidney tubule cells may also be associated with softening of the bones (with bone pain and sometimes resulting in fractures), and decreases in potassium or phosphate in the blood.	the blood of a person whose kidneys are not working normally). Emtricitabine/tenofovir disoproxil should not be given to adolescents with existing kidney problems. Patients should inform their doctor if they have had kidney disease, or if tests have shown problems with their kidneys. The doctor may order blood tests to measure kidney function before starting the treatment and during the treatment to monitor the kidneys and may accordingly advise the patients to take the tablets less often or to stop taking. Prior to initiating emtricitabine/tenofovir disoproxil for the treatment of HIV-1 infection or for use in PrEP, it is recommended that CrCl (a test that helps determine whether the kidneys are functioning normally) is calculated in all individuals. If use of emtricitabine/tenofovir disoproxil along with any other medicine that can damage kidneys is unavoidable, the doctors would monitor patients' kidney function once a week. In patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor (anti HIV medicine) should be carefully evaluated.
Bone events due to damage to the kidney tubule cells/bone loss leading to softening of the bones (Bone events due to proximal renal	Bone problems (sometimes resulting in fractures) may also occur due to damage to kidney tubule cells. Softening of the bones (with bone pain and sometimes resulting in	Patients should inform their doctor If they notice any of the symptoms of bone disorders. Alternative treatment regimens should be considered for patients with osteoporosis (a

Risk	What is known	Preventability
tubulopathy/loss of BMD)	fractures) is rare side effect of emtricitabine/tenofovir disoproxil. Damage to kidney tubule cells may be associated with softening of the bones (with bone pain and sometimes resulting in fractures). Tests may show decreased phosphate levels in the blood.	bone disease that occurs when the body loses too much bone, makes too little bone, or both) that are at a high risk for fractures.
Interaction of emtricitabine/tenofovir disoproxil with a nucleoside analogue antiviral agent used to treat HIV/AIDS (Interaction with didanosine)	Taking emtricitabine/tenofovir disoproxil with other antiviral medicines that contain didanosine (a medicine for HIV) can raise the levels of didanosine in blood and may reduce CD4 cell (type of blood cells which fight against infection in the body) counts. Rarely, pain and swelling 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. Lactic acidosis is a rare but potentially life-threatening side effect. Lactic acidosis occurs more often in women, particularly if they are overweight, and in people with liver disease. The following side effects may be signs of lactic acidosis: • deep rapid breathing • drowsiness • feeling sick (nausea), being sick (vomiting) • stomach pain	Co-administration is not recommended because it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines. The doctor should carefully consider whether to treat patients with combinations of tenofovir and didanosine. Patients should contact their doctor immediately if they experience symptoms of lactic acidosis or think they may have lactic acidosis.
Inflammation of pancreas (Pancreatitis)	Inflammation of the pancreas has been reported when medicines containing tenofovir disoproxil and didanosine were taken together. Pain in the abdomen (tummy) caused by inflammation of the pancreas is an uncommon side effect of emtricitabine/tenofovir disoproxil. Tests may also show problems associated with the pancreas. Increased levels of lipase (the	The doctor should carefully consider whether to treat patients with combinations of tenofovir and didanosine. Patients should inform their doctor If they notice any of the symptoms of pancreatitis.

Risk	What is known	Preventability
	enzyme produced by pancreas) in the blood and pancreatic amylase (an enzyme that helps digest carbohydrates) is a common side effect of emtricitabine/tenofovir disoproxil. If tests are conducted in patients using emtricitabine/tenofovir disoproxil pancreas problems may be seen.	
Development of HIV infection, including infection resulting due to failure in taking a prescribed medication or following a prescribed course of treatment, if used to prevent HIV. (HIV-1 acquisition, including infection resulting from non-adherence (PrEP indication))	The effectiveness of emtricitabine/tenofovir disoproxil in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable medicine levels in blood. If flu-like illness is observed, it could mean that patient might have recently been infected with HIV. Signs of HIV infection include: • tiredness • fever • joint or muscle aches • headache • vomiting or diarrhea • rash • night sweats • enlarged lymph nodes in the neck or groin	You must be HIV negative before you start to take emtricitabine/tenofovir disoproxil to reduce the risk of getting HIV. You must get tested to make sure that you do not already have HIV infection. Do not take emtricitabine/tenofovir disoproxil to reduce your risk unless you are confirmed to be HIV negative. HIV-1 uninfected individuals should be counselled to strictly adhere to the recommended emtricitabine/tenofovir disoproxil dosing schedule. Patient is advised to take emtricitabine/tenofovir disoproxil every day to reduce the risk, not just when he/she thinks that they might have been at risk of HIV infection. Patient should not miss any doses of emtricitabine/tenofovir disoproxil, or stop taking it as it may increase the risk of getting HIV infection. If you think you were infected with HIV, tell your doctor straight away. They may want to do more tests to make sure you are still HIV negative Patient should not change the dose unless told by the doctor. Patient should inform the doctor regarding any flu-like illness

Risk	What is known	Preventability
		either in the month before starting emtricitabine/tenofovir disoproxil, or at any time while taking emtricitabine/tenofovir disoproxil Get tested for HIV regularly. While taking emtricitabine/tenofovir disoproxil to reduce the risk of getting HIV: • Always practice safer sex. Use condoms to reduce contact with semen, vaginal fluids, or blood. • Do not share personal items that can have blood or body fluids on them, such as toothbrushes and razor blades. • Do not share or re-use needles or other injection or drug equipment. • Get tested for other sexually transmitted infections such as syphilis (a chronic bacterial disease that is contracted chiefly by infection during sexual intercourse) and gonorrhea (a disease involving inflammatory discharge from the urethra or vagina). These infections make it easier for HIV to infect you.
Development of a condition where in the virus multiplies even in the presence of a drug due to the decreased drug effectiveness in patients with unidentified or sudden onset of HIV-1 infection, if used to to prevent HIV (Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication))	Emtricitabine/tenofovir disoproxil alone does not constitute a complete regimen for the treatment of HIV-1 and HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who are only taking emtricitabine/tenofovir disoproxil.	You must be HIV negative before you start to take emtricitabine/tenofovir disoproxil to reduce the risk of getting HIV. You must get tested to make sure that you do not already have HIV infection. Do not take emtricitabine/tenofovir disoproxil to reduce your risk unless you are confirmed to be HIV negative. Patient should always take the dose recommended by the doctor to make sure that

Risk	What is known	Preventability
		the medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Patient should not change the dose unless told by the doctor. If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, use of emtricitabine/tenofovir disoproxil should be delayed for at least one month and HIV-1 status reconfirmed before starting emtricitabine/tenofovir disoproxil for PrEP. While taking emtricitabine/tenofovir disoproxil to reduce the risk of getting HIV: • Always practice safer sex. Use condoms to reduce contact with semen, vaginal fluids, or blood. • Do not share personal items that can have blood or body fluids on them, such as toothbrushes and razor blades. • Do not share or re-use needles or other injection or drug equipment. • Get tested for other sexually transmitted infections such as syphilis and gonorrhea. These infections make it easier for HIV to infect you.

Table 5-6 Important potential risks

None

Table 5-7 Missing information

Risk	What is known
Safety in children (including long-term safety)	Emtricitabine/tenofovir disoproxil is not for use in children under 12 years of age.

Risk	What is known
	Patients should inform their doctor if they notice following symptoms: • Children given emtricitabine very commonly experienced changes in skin colour including darkening of the skin in patches • Children commonly experienced low red blood cell count causing the child to be tired or breathless This medicine should be kept out of the sight and reach of children.
Safety in elderly patients	Patients should talk to their doctor if they are over 65 years of age before taking emtricitabine/tenofovir disoproxil. Emtricitabine/tenofovir disoproxil has not been studied in patients over 65 years of age so the doctor should monitor such patients carefully when the medicine is prescribed to them.
Safety in pregnancy	If patients are pregnant, think they might be pregnant or are planning to have a baby, they should consult the doctor or pharmacist before taking this medicine. Patients should not take emtricitabine/tenofovir disoproxil during pregnancy unless specifically discussed with their doctor. Although there are limited clinical data on the use of emtricitabine/tenofovir disoprixil in pregnant women, it is not usually used unless absolutely necessary. If patients are women who could get pregnant during treatment with emtricitabine/tenofovir disoproxil, they must use an effective method of contraception to avoid becoming pregnant. If patients become pregnant, or plan to become pregnant, they should ask their doctor about the potential benefits and risks of therapy with emtricitabine/tenofovir disoproxil to them and their child. If patients have taken emtricitabine/tenofovir disoproxil during pregnancy, their doctor might request regular blood tests and other diagnostic tests to monitor the development of their child. In children whose mothers took NRTIs (group of anti HIV medicines) during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.
Safety in breast-feeding (Safety in lactation)	If patients are breast-feeding they should ask their doctor or pharmacist for advice before taking emtricitabine/tenofovir disoproxil. Patients should not breast-feed during treatment with emtricitabine/tenofovir disoproxil because the active substances in this medicine pass into human breast milk. If a woman has HIV it is recommended that she should not

Risk	What is known
	breast-feed, to avoid passing the virus to the baby in breast milk.
Safety in patients with abnormally reduced kidney function (Safety in patients with renal impairment)	Renal safety with emtricitabine/tenofovir disoproxil has only been studied to a very limited degree in patients with impaired renal function (CrCl <80 ml/min). Dose interval adjustments are recommended for patients with CrCl 30 49 ml/min. Emtricitabine/tenofovir disoproxil has not been studied in HIV-1 uninfected individuals with CrCl < 60 mL/min and is therefore not recommended for use in this population. Emtricitabine/tenofovir disoproxil may affect kidneys so it is not recommended if patients have severe kidney disease or are receiving hemodialysis (a process of purifying the blood of a person whose kidneys are not working normally). Patients should inform their doctor if they have had kidney disease, or if tests have shown problems with their kidneys. Emtricitabine/tenofovir disoproxil should not be given to adolescents with existing kidney problems. The doctor may order blood tests to assess kidney function before starting the treatment and during the treatment to monitor the kidneys and may accordingly advise the patients to take the tablets less often. In individual patients at risk for renal impairment disease, the use of tenofovir disoproxil with a boosted protease inhibitor (anti HIV medicine) should be carefully evaluated. If serum phosphate is <1.5 mg/dl (0.48 mmol/l) or CrCl is decreased to <50 ml/min in any patient receiving emtricitabine/tenofovir disoproxil, renal function should be reevaluated within 1 week, including measurements of blood glucose, blood potassium and urine glucose concentrations.

Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs 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 package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has the following additional risk minimization measures.

Table 5-8 Renal toxicity

Risk minimization measure(s)

Risk minimization measure(s)

Summary description of main additional risk minimization measures:

- Renal monitoring tool (adult patients)
- Renal monitoring brochure (pediatric patients)

Objective and rationale: To minimize the risk of toxicity to kidneys with use of this medicinal product.

Proposed action: Provision of Renal monitoring tool (adult patients) and Renal monitoring brochure (pediatric patients)

This educational material will be provided to prescribing physicians to convey the following key messages:

Renal monitoring tool (adult patients) includes:

- Important Points to Consider
- Tenofovir disoproxil renal safety profile (data)
- Monitoring of kidney function
- Use in kidney dysfunction

Renal monitoring brochure (pediatric patients) includes:

- Important points to consider
- Management of kidney effects
- Management of bone effects
- Dosing recommendations for emtricitabine/tenofovir disoproxil in children and adolescents

Table 5-9 HIV-1 acquisition, including infection resulting from non-adherence (PrEP indication)

Risk minimization measure(s)

Summary description of main additional risk minimization measures:

PrEP educational brochure for prescribers entitled 'Important Safety Information for Prescribers about emtricitabine/tenofovir disoproxil for a PrEP Indication', PrEP Checklist for prescribers, PrEP educational brochure for the individual at risk entitled 'Important Information about Emtricitabine/tenofovir disoproxil to Reduce the Risk of getting HIV Infection', PrEP reminder card

Objective and rationale: To minimize the risk related to HIV-1 acquisition, including infection resulting from non-adherence

Proposed action: Provision of PrEP educational brochure for prescribers entitled 'Important Safety Information for Prescribers about emtricitabine/tenofovir disoproxil for a PrEP Indication', PrEP Checklist for prescribers, PrEP educational brochure for the individual at risk entitled 'Important Information about emtricitabine/tenofovir disoproxil to Reduce the Risk of getting HIV Infection', PrEP reminder card.

These education materials will be provided to prescribing physicians to convey the following key messages:

PrEP educational brochure for prescribers includes

- Reminder of the key safety information regarding the use of emtricitabine/tenofovir disoproxil for PrEP
- Reminder of factors to help identify individuals at high risk of acquiring HIV-1
- Reminder on the risk of development of HIV-1 drug resistance in undiagnosed HIV-1–Infected individuals
- Provides safety information on adherence, HIV testing, renal, bone and HBV status

PrEP Checklist for prescribers includes

- Reminders for evaluations/counselling at the initial visit and follow-up.

Risk minimization measure(s)

PrEP educational brochure for the individual at risk (to be provided by HCP) includes

- Reminders on what the individual should know before and while taking emtricitabine/tenofovir disoproxil to reduce the risk of getting HIV infection
- Reminder on the importance of strict adherence to the recommended dosing regimen
- Provides information on how to take emtricitabine/tenofovir disoproxil
- Provides information on the possible side effects
- Provides information on how to store emtricitabine/tenofovir disoproxil

PrEP reminder card for the individual at risk (to be provided by HCP) includes

- Reminders to adhere to the dosing schedule
- Reminder to attend scheduled clinic visits

Table 5-10 Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication)

Risk minimization measure(s)

Summary description of main additional risk minimization measures:

PrEP educational brochure for prescribers entitled 'Important Safety Information for Prescribers about emtricitabine/tenofovir disoproxil for a PrEP Indication', PrEP Checklist for prescribers, PrEP educational brochure for the individual at risk entitled 'Important Information about emtricitabine/tenofovir disoproxil to Reduce the Risk of getting HIV Infection', PrEP reminder card

Objective and rationale: To minimize the risk related to development of resistance in patients with unrecognized or acute HIV-1 infection

Proposed action: Provision of PrEP educational brochure for prescribers entitled 'Important Safety Information for Prescribers about emtricitabine/tenofovir disoproxil for a PrEP Indication', PrEP Checklist for prescribers, PrEP educational brochure for the individual at risk entitled 'Important Information about emtricitabine/tenofovir disoproxil to Reduce the Risk of getting HIV Infection', PrEP reminder card.

These education materials will be provided to prescribing physicians to convey the following key messages:

PrEP educational brochure for prescribers includes

- Reminder of the key safety information regarding the use of emtricitabine/tenofovir disoproxil for PrEP
- Reminder of factors to help identify individuals at high risk of acquiring HIV-1
- Reminder on the risk of development of HIV-1 drug resistance in undiagnosed HIV-1–Infected individuals
- Provides safety information on adherence, HIV testing, renal, bone and HBV status

PrEP Checklist for prescribers includes

- Reminders for evaluations/counselling at the initial visit and follow-up.

PrEP educational brochure for the individual at risk (to be provided by HCP) includes

- Reminders on what the individual should know before and while taking emtricitabine/tenofovir disoproxil to reduce the risk of getting HIV infection
- Reminder on the importance of strict adherence to the recommended dosing regimen
- Provides information on how to take emtricitabine/tenofovir disoproxil
- Provides information on the possible side effects
- Provides information on how to store emtricitabine/tenofovir disoproxil

PrEP reminder card for the individual at risk (to be provided by HCP) includes

- Reminders to adhere to the dosing schedule
- Reminder to attend scheduled clinic visits

Part VI.2.6 Planned post authorization development plan

None

Part VI.2.7 Summary of changes to the Risk Management Plan over time

Table 5-11 Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.1	25 Jan 2018	None	Addition of educational material 'Renal management brochure (pediatric patients)' as additional risk minimization measure for safety concern "renal toxicity" in the RMP as the product information has been updated for the extension of the indication to pediatric patients. The information of RMP was ammended as per the updated SmPC and PL
2.0	24 Apr 2017	Renal toxicity	Deletion of educational material "HCP guide: Chronic hepatitis B adolescents", "HCP guide: Chronic hepatitis B adults, "HCP guide: HIV-1 children and adolescents" as the Sandoz product does not include the respective indications (Hepatitis B and HIV in children and adolescents).