VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

HIV is a virus that attacks the immune system (the body's natural defences) and weakens it by destroying certain white blood cells (called CD4 T cells), which are important for protecting the body against various bacteria, viruses and other germs. If left untreated, the HIV virus multiplies and the body becomes increasingly unable to fight infections and disease.

In 2011, 34 million people worldwide were living with HIV, including 900,000 in Western and Central Europe and 1.4 million in Eastern Europe and Central Asia. In 2011, 2.5 million people were newly infected with HIV, down by one-fifth (20%) compared with 2001.

VI.2.2 Summary of treatment benefits

Efavirenz/emtricitabine/tenofovir is an antiviral medicine which is used to treat HIV. It works by interfering with the normal working of enzymes that are essential for the viruses to reproduce themselves. This medicine is not a cure for HIV infection. While taking efavirenz/emtricitabine/tenofovir you may still develop infections or other illnesses associated with HIV infection. You can also pass on HIV to others, so it is important to take precautions to avoid infecting other people. If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, efavirenz/emtricitabine/tenofovir can be considered effective in the approved indication.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Kidney toxicity (Renal Toxicity)	Efavirenz/emtricitabine/tenofovir may affect your kidneys. Efavirenz/emtricitabine/tenofovir is not usually taken with other medicines that can damage your kidneys. If this is unavoidable, your doctor will monitor your kidney function once a week.	Before starting treatment, your doctor may order blood tests to assess kidney function. Your doctor may also order blood tests during treatment to monitor your kidneys.
Bone problems (Bone events due to proximal renal tubulopathy/loss of BMD)	Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Bone problems (sometimes resulting in fractures) may also occur due to damage to kidney tubule cells.	Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Risk	What is known	Preventability
Psychiatric and nervous system symptoms	Psychiatric side effects have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk. Reported side effects include severe depression, death by suicide, delusions and psychotic behaviour.	Psychiatric symptoms: Patients are advised that if they experience symptoms such as severe depression, psychosis, or thoughts of suicide, they should contact their doctor immediately. If the doctor believes the symptoms are related to the use of efavirenz/emtricitabine/tenofovir, then patients should discuss alternative treatment options with their doctor. Nervous system symptoms: Side effects may occur more frequently when efavirenz/emtricitabine/tenofovir is taken concurrently with meals. Therefore, efavirenz/emtricitabine/tenofovir should be taken on an empty stomach, preferably at bedtime.
Skin rash and severe skin reactions (Skin rash and skin reactions (including Stevens-Johnson syndrome, TEN and erythema multiforme))	Rashes may be caused by efavirenz/emtricitabine/tenofovir.	If you see any signs of a severe rash with blistering or fever, stop taking efavirenz/emtricitabine/tenofovir and tell your doctor at once. If you had a rash while taking another NNRTI, you may be at higher risk of getting a rash with efavirenz/emtricitabine/tenofovir
Liver events (High grade hepatic enzyme elevation and severe hepatic events)	The following side effects are rare (these may affect up to 1 in every 1,000 patients): liver failure, in some cases leading to death or liver transplant. Most cases occurred in patients who already had liver disease, but there have been a few reports in patients without any existing liver disease.	Tell your doctor if you have a history of liver disease, including chronic active hepatitis. Patients with liver disease including chronic hepatitis B or C, who are treated with combination antiretrovirals, have a higher risk of severe and potentially life-threatening liver problems. Your doctor may conduct blood tests in order to check how well your liver is working or may switch you to another medicine. If you have severe liver disease, do not take efavirenz/emtricitabine/tenofovir

Risk	What is known	Preventability
Spinal cord and brain birth defects (Neural tube developmental abnormalities)	Defects were observed in 3 of 20 newborn monkeys treated with efavirenz, which included abnormal development of the brain and bones of the skull, absence of one or more eyes, small eyes, and cleft palate. In pregnant rats, efavirenz can induce early death of the foetus by breaking down the embryo and completely absorbing the products of the conception.	Folic acid taken before conception appears to reduce the risk of spinal cord and brain birth defects in the general population. In HIV infected females of childbearing age, adequate contraceptive measures are strongly recommended to minimize the risk of accidental exposure in the first trimester of pregnancy. Efavirenz/emtricitabine/tenofovir should be used during pregnancy only if the potential benefit justifies the potential risk to the unborn child, such as in pregnant women without other therapeutic options. Women of childbearing age should undergo pregnancy testing before starting efavirenz/emtricitabine/tenofovir. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Also, use of adequate contraceptive measures should continue for 12 weeks after stopping efavirenz/emtricitabine/tenofovir

Risk	What is known	Preventability
Worsening of hepatitis after treatment discontinuation (Post-treatment hepatic flares in HIV/HBV co-infected patients)	Efavirenz/emtricitabine/tenofovir shows some activity against hepatitis B virus although emtricitabine is not approved for the treatment of hepatitis B infection. Symptoms of your hepatitis may become worse after discontinuation of efavirenz/emtricitabine/tenofovir. Your doctor may then conduct blood tests at regular intervals in order to check how well your liver is working.	If you have both HIV infection and hepatitis B, it is especially important not to stop your Efavirenz/emtricitabine/tenofovir treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping emtricitabine or tenofovir disoproxil (two of the three components of efavirenz/emtricitabine/tenofovir). If efavirenz/emtricitabine/tenofovir is stopped your doctor may recommend that you resume hepatitis B treatment. You may require blood tests to check how your liver is working for 4 months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening. Tell your doctor immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

Risk	What is known	Preventability
Interaction with didanosine	Efavirenz/emtricitabine/tenofovir may interact with other medicines As a result; the amounts of efavirenz/emtricitabine/tenofovir or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels.	It is important to tell your doctor or pharmacist if you are taking any medicines containing didanosine (for HIV infection): Taking efavirenz/emtricitabine/tenofovir with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, have been reported rarely when medicines containing tenofovir disoproxil and didanosine were taken together. Your doctor will carefully consider whether to treat you with medicines containing tenofovir and didanosine.

Risk	What is known	Preventability
Change of medicinal product blood levels (Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms)	In patients with a specific genetic variation called CYP2B6 genetic polymorphism, exposure to components of efavirenz/emtricitabine/tenofovir may be increased.	The distribution of this genetic characteristic is such that no single variable (e.g., gender, race, or age) would appear to be predictive of the risk. Also, there was no clear pattern of risk even among patients with the same genetic characteristic. The efavirenz/emtricitabine/tenofovir SmPC specifically warns consumers about this genetic characteristic. Although a relationship between this genetic characteristic and increased frequency and severity of efavirenz-associated side-effects is unknown, the potential for a causal relationship cannot be excluded. Efavirenz/emtricitabine/tenofovir is highly recommended to be taken on an empty stomach (preferably at bedtime) in people with this genetic characteristic because food may also increase levels of efavirenz in the bloodstream. Increased levels of efavirenz may lead to increased frequencies of undesirable side-effects.
Pancreas problems (inflammation of the pancreas) (Pancreatitis)	The tenofovir component of efavirenz/emtricitabine/tenofovir has been associated with a side effect of pancreatitis. The risk of pancreatitis is low: in clinical trials involving tenofovir DF, the frequency of pancreatitis was 0.2% (l in 500 patients).	By awareness of the potential for pancreatitis, as described in the efavirenz/emtricitabine/tenofovir SmPC and PIL, and by the doctor considering stopping treatment if necessary.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Lack of efficacy	If a patient was using a protease-inhibitors based regimen, after switching to efavirenz/emtricitabine/tenofovir a decreased response to therapy may appear and these patients should be carefully monitored for viral load.

Risk	What is known (Including reason why it is considered a potential risk)
Overdose	An overdose of efavirenz/emtricitabine/tenofovir can occur if a patient takes or a doctor accidentally prescribes more than one dose of efavirenz/emtricitabine/tenofovir a day, or if a patient takes or a doctor prescribes efavirenz/emtricitabine/tenofovir along with other anti-HIV medicines that contain one or more of the active ingredients of efavirenz/emtricitabine/tenofovir. Only isolated reports of overdose, occurring through accidental use of efavirenz/emtricitabine/tenofovir at the same time as any of its active ingredients have been received. The efavirenz/emtricitabine/tenofovir SmPC and PIL contain clear warnings that efavirenz/emtricitabine/tenofovir should not be taken with other medicines containing the same active ingredients.
Kidney stones (Urolithiasis/ nephrolithiasis)	Serious and non-serious reports of stone-related side-effects have been reported in patients treated with the efavirenz component of the reference product. The majority of reports involved patients with a prior history of kidney stones and/or concurrent exposure to other medicines with stone-formation potential. Estimates of frequency of this side effect cannot be made.
Cancer (Malignant neoplasms)	No evidence of an increased risk of cancer in patients using efavirenz-containing products (including efavirenz/emtricitabine/tenofovir) has been established. The potential risk of cancercaused by usingthese products does not appear to be measurably increased compared to other anti-HIV medicines.

Missing information

Risk	What is known
Safety in children (<3 months old for efavirenz, including long-term safety for tenofovir)	Since the use of efavirenz/emtricitabine/tenofovir in children and adolescents has not been studied, efavirenz/emtricitabine/tenofovir should not be given to children and adolescents under 18 years of age.
Safety in elderly patients	Insufficient numbers of patients over 65 years of age have been studied. If you are over 65 years of age and are prescribed efavirenz/emtricitabine/tenofovir your doctor will monitor you carefully.
Safety in pregnancy	Serious birth defects have been seen in unborn animals and in the babies of women treated with efavirenz during pregnancy. If you have taken efavirenz/emtricitabine/tenofovir during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. Ask your doctor or pharmacist for advice before taking any medicine.
Safety in lactation	HIV may be carried through the breast milk to the infant during nursing. Efavirenz, emtricitabine and tenofovir have been shown to pass into human breast milk. It is recommended that mothers with HIV infection do not breastfeed their infants.

Risk	What is known
Safety in patient with liver problems (hepatic impairment)	Patients with liver disease including chronic hepatitis B or C, who are treated with combination antiretrovirals, have a higher risk of severe and potentially life-threatening liver problems. Your doctor may conduct blood tests in order to check how well your liver is working or may switch you to another medicine.
Safety in patients with kidney problems (renal impairment)	Efavirenz/emtricitabine/tenofovir is not recommended if you have moderate to severe kidney disease. Efavirenz/emtricitabine/tenofovir may affect your kidneys. Before starting treatment, your doctor may order blood tests to assess kidney function. Your doctor may also order blood tests during treatment to monitor your kidneys.

VI.2.5 Summary of 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 minimising them. An abbreviated version of this in lay language is provided in the form of the Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

In addition, this medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Kidney toxicity (Renal Toxicity)

Risk minimisation measure(s)
Objective and rationale: To bring to the attention of the treating physicians on the risk of renal disease associated with tenofovir disoproxil and to emphasize the importance of regular monitoring of renal function during tenofovir disoproxil therapy.
– The following key elements will be included in the educational material:That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products – Medicinal product is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min) – That use of medicinal product should be avoided with concomitant or recent use of nephrotoxic medicinal products. If medicinal product is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule. – That patients should have their baseline renal function assessed prior to initiating therapy – The importance of regular monitoring of renal function during therapy – Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment – If serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to <50 ml/min then renal function must be re-evaluated within one week. If creatinine clearance is confirmed as <50 ml/min or serum phosphate decreases to < 1.0 mg/dl then therapy should be interrupted. Interrupting treatment with medicinal product should also be considered in

Risk minimisation measure(s)
case of progressive decline of renal function when no other cause has been identified. – Instructions on the use of the creatinine clearance slide ruler
Proposed action: • HIV renal educational brochure, including the creatinine clearance slide ruler

VI.2.6 Planned post-authorisation development plan

Study / activity	Objectives	Safety concerns addressed	Status	Planned date for submission of (interim and) final results
Antiretroviral pregnancy registry (APR)	Objective of the APR is to detect any major teratogenic effect involving any of the Registry drugs when administered to pregnant women	Use in pregnancy	In progress	Regular APR reports. Estimated study completion date- January 2099

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

Not applicable for pre-approval versions.