VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Human immunodeficiency virus (HIV) is a virus that attacks the immune system, and weakens the body's ability to fight infections and disease. A person with HIV is considered to have developed acquired immune deficiency syndrome (AIDS) when the immune system is so weak it can no longer fight off a range of diseases with which it would normally cope.

Globally around 31 million adults and 3 million children were living with HIV to the end of 2011. The number of infected individuals varies enormously by geographical region. Sub Saharan Africa is most severely affected.

HIV infection remains a life-threatening disease in infected persons who do not receive adequate treatment. The number of people dying from causes related to AIDS has declined because of an increase in the availability of treatments for HIV. Most people who die from AIDS are from sub-Saharan Africa.

VI.2.2 Summary of treatment benefits

The once-daily triple combination therapy with efavirenz, emtricitabine and tenofovir DF (including the single-tablet regimen) is effective in maintaining virological suppression and is generally well tolerated, according to several clinical trials. Moreover, additional data from some of these studies indicate that adherence to treatment was maintained or improved after switching to the once-daily triple combination.

Thus, the efavirenz/emtricitabine/tenofovir DF single-tablet regimen provides a convenient once-daily regimen for use in treatment-experienced adults that may confer an advantage over more complex or frequently administered regimens for which adherence to treatment is an issue. [1]

VI.2.3 Unknowns relating to treatment benefits

This medicinal product (which contains three active ingredients, efavirenz, emtricitabine and tenofovir DF) is a fixed dose combination tablet and is not considered an appropriate tablet to use in children and adolescents under 18 years old who may need weight or age-based modification of the individual active ingredients.

Clinical trials with efavirenz, emtricitabine and tenofovir DF did not include enough patients 65 years of age and older to determine whether elderly patients respond differently than younger patients. Elderly patients are more likely to have other diseases, including problems with their liver and kidneys, and to take other medicines.

Women should not get pregnant during treatment with this medicinal product or for 12 weeks after stopping treatment. Birth defects have been seen in unborn animals and in the babies of women treated with efavirenz (one of the active ingredients of this medicinal product).

HIV may be carried through the breast milk to the infant during nursing. Efavirenz, emtricitabine and tenofovir DF have been shown to pass into human breast milk. It is recommended that mothers with HIV infection do not breastfeed their infants.

Patients with chronic hepatitis B or C and treated with anit-HIV medicines are at increased risk for severe and potentially fatal liver events. Patients with pre-existing liver problems have an increased frequency of liver function problems during anti-HIV therapy and should be monitored

during therapy with this medicinal product. This medicinal product must not be used in patients with severe liver problems and is not recommended in patients with moderate liver problems.

The tenofovir DF component of this medicinal product is removed from the blood by the kidney and the amount of tenofovir increases in patients with kidney problems. This medicinal product is not recommended for patients with moderate to severe kidney disease, as the dose of the emtricitabine and tenofovir DF components of this product would need to be adjusted in these patients and this cannot be achieved with the combination tablet.

VI.2.4 Summary of safety concerns

Important identified risks:

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 behavior.	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 this product, then patients should discuss alternative treatment options with their doctor. Nervous system symptoms: Side-effects may occur more frequently when this product is taken concurrently with meals. Therefore, efavirenz/ emtricitabine/ tenofovir product should be taken on an empty stomach, preferably at bedtime.
Skin rashes and severe skin reactions	Mild-to-moderate rash has been reported in clinical trials with efavirenz and usually goes away with continued therapy.	If efavirenz/emtricitabine/ tenofovir product is restarted in a patient who stopped therapy because of rash, use of

	Severe rash associated with blistering or ulceration has been reported in < 1% of adults treated with efavirenz. The frequency of severe skin rashes in adults treated with efavirenz was 0.1 %. In children, rash was observed in 58 of 182 children (32%) and severe rash was observed in 6 children (3%).	appropriate allergy medicines is recommended. Efavirenz/ emtricitabine/ tenofovir product is not recommended for patients who have had a life-threatening skin reaction.
Liver disease ***(High-grade hepatic enzymes elevation and severe hepatic events)***	Most patients with liver function changes do not show symptoms. Since liver function changes can also be a sign of hepatitis, elevations in liver enzymes in particular must be monitored. Liver failure can occur in patients with no pre-existing liver disease or other known risk factors.	Patients with underlying liver disease should be tested regularly to prevent potential liver damage until the side-effects go away. Patients without pre-existing liver disorders or other risk factors should also be considered for periodic monitoring of liver enzymes.
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 fetus by breaking down the embryo and completely absorbing the products of the conception. As of 31 January 2011, 18	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 product should be used during pregnancy only if the potential

	reports of defects in 735 human infants with first trimester exposure to efavirenz have been received, via a registry regarding use of antiretrovirals during pregnancy. These defects included a single case of unclosed backbone/spinal canal and a single case of eye deformities with severe slanted facial clefts and abnormal limbs which were constricted during development.	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 product. 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 product.
Higher levels of efavirenz in the bloodstream caused by a genetic characteristic ***(Alteration in efavirenz blood levels and CYP2B6 genetic polymorphisms)***	Patients with a particular genetic characteristic (homozygous G516T genetic variant of the CYP2B6 isozyme) may tend to have increased levels of efavirenz in their blood stream.	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 Summary of Product Characteristics (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 product 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 increasedfrequencies of undesirable side-effects.
Liver problems (flare-up of hepatitis) in patients infected with both HIV - 1 and hepatitis B (HBV) who stop treatment with EFV/FTC/TDF ***(Post-treatment hepatic flares in HIV-1/HBV coinfected patients)***	Two of the 3 medicines that make up this product (emtricitabine and tenofovir DF) are anti-HBV medicines as well as anti-HIV medicines. A flare up of hepatitis B is a risk with stopping any antiviral medicine that works against HBV. Stopping efavirenz/ emtricitabine/ tenofovir product in patients who also have HBV infection can lead to worsening of liver problems (flare-up of hepatitis).	Yes, by not stopping efavirenz/emtricitabine/ tenofovir treatment without talking to a doctor first, and by switching to another anti-HBV therapy or closely monitoring the patient for worsening of liver problems if treatment is stopped.
Kidney problems ***(Renal toxicity)***	The tenofovir DF component of this product has been associated with kidney problems, including damage to kidney tubule cells, kidney failure, kidney inflammation, passing a lot of urine, and increases in creatinine in blood. The frequency of renal events is very low: in clinical trials	Yes, by carrying out blood tests for kidney function at the start of treatment and during treatment with efavirenz/ emtricitabine/ tenofovir product, by avoiding use of other medicines that may damage the kidneys, and by the doctor considering stopping treatment if necessary.

	involving tenofovir DF, the frequency of increased creatinine was 0.2% (1 in 500 patients) and of kidney failure was 0.06% (3 in 5000 patients). Risk factors for kidney problems include advanced HIV disease (low CD4 count at the start of treatment), low weight, older age, kidney problems before starting therapy, use of other medicines that are damaging to kidneys, high blood pressure, and also being infected with hepatitis C.	
Bone problems ***(Bone events due to proximal renal tubulopathy/loss of bone mineral density)***	Damage to kidney tubule cells associated with the tenofovir DF component of this product can cause bone softening (with bone pain and sometimes resulting in fractures). The frequency of bone softening is low; in clinical trials of tenofovir DF, no side effects of bone softening were observed (out of 1633 patients receiving tenofovir DF). Thinning of bones (decreases in bone mineral density) have also been observed in patients treated with tenofovir DF. However, the clinical significance is unknown as no increase in fracture rates has been observed.	Yes, by awareness of the potential for bone problems, as described in the SmPC and PIL, and by monitoring for renal function at the start of treatment and during treatment.

Drug interaction with the anti-HIV medicine didanosine ***(Interaction with didanosine)***	If the tenofovir DF component of this product and didanosine are taken together, the levels of didanosine in the blood can increase, which may increase the risk of side effects associated with didanosine. However, given that didanosine is no longer a recommended anti-HIV medicine, the likelihood of the two medicines being taken together is low.	Yes, by avoiding use of didanosine with this product.
Pancreas problems (inflammation of the pancreas) ***(Pancreatitis)***	The tenofovir DF component of this product 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% (1 in 500 patients).	Yes, by awareness of the potential for pancreatitis, as described in the 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 effectiveness ***(Lack of efficacy)***	As tenofovir DF levels in the blood are increased by the presence of food, there is a possibility that as this medicinal product is recommended to be taken on an empty stomach, the levels of tenofovir DF will be reduced.
Overdose	An overdose of this medicinal product can occur if a patient takes or a doctor accidentally prescribes more than one dose of this medicinal product a day, or if a patient takes or a doctor prescribes this medicinal product along with other anti-HIV medicines that contain one or more of the active

	ingredient of this medicinal product. The SmPC and PIL contain clear warnings that this medicinal product 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 this medicinal product. The majority of reports were involved patients with a prior history of kidney stones and/or concurrent exposure to other medicines with stone-formation potential. A few literature reports identified kidney stones with efavirenz-containing medicines. There were no reports with a fatal outcome. Cases of kidney stones have been reported during post-marketing monitoring in HIV patients taking efavirenz. Because these side-effects were reported voluntarily during clinical practice, estimates of frequency cannot be made in the post marketing reporting system.
Cancer ***(Malignant neoplasms)***	The potential human risk of cancer-related side-effects from efavirenz-containing products does not appear to be measurably increased compared to other anti-HIV medicines. In fact, no evidence of an increased risk of cancer in patients using these products has been established.

Missing information:

Risk	**What is known**
Safety in children (including long-term safety)	This medicinal product (which contains three active ingredients, efavirenz, emtricitabine and tenofovir DF) is a fixed dose combination tablet and is not considered an appropriate tablet to use in children and adolescents under 18 years old who may need weight or age-based modification of the individual active

Risk	What is known
	ingredients.
Safety in elderly patients	Clinical trials with efavirenz, emtricitabine and tenofovir DF did not include enough patients 65 years of age and older to determine whether elderly patients respond differently than younger patients. Elderly patients are more likely to have other diseases, including problems with their liver and kidneys, and to take other medicines.
Safety in pregnancy	Women should not get pregnant during treatment with this medicinal product or for 12 weeks after stopping treatment. Birth defects have been seen in unborn animals and in the babies of women treated with efavirenz (one of the active ingredients of this medicinal product).
Safety during breastfeeding ***(Safety in lactation)***	HIV may be carried through the breast milk to the infant during nursing. Efavirenz, emtricitabine and tenofovir DF have been shown to pass into human breast milk. It is recommended that mothers with HIV infection do not breastfeed their infants.
Safety in patients with liver problems ***(Safety in patients with hepatic impairment)***	Patients with chronic hepatitis B or C and treated with anit-HIV medicines are at increased risk for severe and potentially fatal liver events. Patients with pre-existing liver problems have an increased frequency of liver function problems during anti-HIV therapy and should be monitored during therapy with this medicinal product. This medicinal product must not be used in patients with severe liver problems and is not recommended in patients with moderate liver problems.
Safety in patients with kidney problems ***(Safety in patients with renal impairment)***	The tenofovir DF component of this medicinal product is removed from the blood by the kidney and the amount of tenofovir increases in patients with kidney problems. This medicinal product is not recommended for patients with moderate to severe kidney disease, as the dose of the emtricitabine and tenofovir DF components of this product would need to be adjusted in these patients and this cannot be achieved with the combination tablet.

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

All medicinal products 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 Package Leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The SmPC and PL of the medicinal product will always be in line with the innovator.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). 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:

Safety concern: *Kidney Problems*
Risk minimisation measures: Physician education
Objective and rationale: • Physicians treating patients with HIV to help them understand the risk of kidney problems with the tenofovir DF component of this medicinal product and the appropriate management of patients to minimize the occurrence and the severity of this risk.
Main additional risk minimisation measure(s): Education program to be provided to prescribing physicians: • "HIV and the Kidney" educational program • HIV kidney educational brochure (including advice on monitoring kidney function)

VI.2.6 Planned post authorisation development plan

Not applicable

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

Not applicable