Emtricitabine / Tenofovir disoproxil Stada 200 mg/245 mg film-coated tablets

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PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

Emtricitabine / Tenofovir disoproxil Stada 200 mg/245 mg film-coated tablets

VI.2.1 Overview of disease epidemiology

HIV-1 infection

In this decade, the global prevalence of HIV-1 infection stabilized at 0.8%. However, the overall number of people living with HIV increased as new infections continued to occur and AIDS deaths were prevented by increasingly available highly effective antiretroviral treatment (ART). Globally, there were an estimated 33.2 million people living with HIV infection or AIDS in 2007, an increase from 29.5 million in 2001. The annual incidence of new HIV infections declined from an estimated 3.0 million in 2001 to an estimated 2.7 million in 2007. There were an estimated 2.0 million HIV-related deaths in 2007. This number represents an increase from 1.7 million deaths in 2001, but as access to treatment increased in this decade, the annual numbers of deaths peaked in 2005 and subsequently decreased. From 2002 to 2007, the number of people receiving ART in developing countries increased from 300 000 to 3.0 million, which was 31% of those who needed treatment.

Heterosexual spread in the general population is the main mode of transmission in sub-Saharan Africa, which remains the most heavily affected region, with 67% of the global burden. Male–male sex, injection drug use, and sex work are the predominant risk factors in most other regions. Infection rates are declining in some regions, including some of the most heavily affected countries in Africa, but climbing elsewhere such as in eastern Europe and central Asia.

In 2009, the United Nations Estimated that 33.2 Million People worldwide were living with human immunodeficiency virus type 1 (HIV-1) infection and that 2.6 million people had been newly infected.

VI.2.2 Summary of treatment benefits

The treatment of human immunodeficiency virus (HIV) disease depends on the stage of the disease and any concomitant opportunistic infections. In general, the goal of treatment is to prevent the immune system from deteriorating to the point that opportunistic infections become more likely.

Tenofovir/emtricitabine (TDF-FTC) is indicated in combination with other ART agents (eg,NNRTIs, PIs) for the treatment of HIV-1 infection in adults and pediatric patients aged 18 years or older.

There is sufficient data to recommend the use of TDF-FTC in the treatment of HIV. It is recommended as a preferred and alternative treatment of choice in both treatment-naïve and experienced patients. In addition to its demonstrated efficacy, TDF-FTC also provides significant advantages in terms of few side effects, low long-term toxicity, once daily dosing and few drug interactions.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of emtricitabine/tenofovir for children below 18 years of age have not been established due to insufficient available safety data. Therefore, emtricitabine and tenofovir disoproxil is not recommended in this population.

Emtricitabine and tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with emtricitabine and tenofovir disoproxil.

Only a moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) are available that indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil. Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity. Therefore the use of Emtricitabine and tenofovir disoproxil may be considered during pregnancy, if necessary.

Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore emtricitabine/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.

There are limited data on the safety and efficacy of emtricitabine and tenofovir disoproxil in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long-term safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in patients with renal impairment emtricitabine and tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Post-treatment hepatic flares in HIV/HBV coinfected patients	Discontinuation of emtricitabine and tenofovir disoproxiltherapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.	Patients co-infected with HIV and HBV who discontinue emtricitabine and tenofovir disoproxil should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.
Severe hepatomegaly with steatosis	Hepatomegaly (liver enlargment) with steatosis (accumulation of fat in the liver) may rarely occur (in up to 1 in 1,000 patients).	Monitoring of liver function tests is recommended.
Renal toxicity	Emtricitabine and tenofovir are primarily excreted by the	It is recommended that creatinine clearance is

	kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil in clinical practice	calculated in all patients prior to initiating therapy with emtricitabine and tenofovir disoproxil and renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients at risk for renal impairment, a more frequent monitoring of renal function is required.
Bone events due to proximal renal tubulopathy/loss of BMD	Tenofovir may cause a reduction in bone mineral density (BMD). The effects of tenofovir disoproxil - associated changes in BMD on long-term bone health and future fracture risk are currently unknown. Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.	If bone abnormalities are detected or suspected, consultation should be obtained.
Interaction with didanosine	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within	Co-administration of tenofovir disoproxil and didanosine is not recommended.

	several tested combinations.	
Pancreatitis	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.	Co-administration of tenofovir disoproxil and didanosine is not recommended.

Missing information

Risk	What is known
Safety in children (including long- term safety)	The safety and efficacy of emtricitabine and tenofovir disoproxil in children under the age of 18 years have not been established. Insufficient safety data are available for children below 18 years of age. Emtricitabine and tenofovir disoproxil is not recommended in this population.
Safety in elderly patients	Emtricitabine and tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with emtricitabine and tenofovir disoproxil.
Safety in pregnancy	A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil. Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity. Therefore the use of Emtricitabine and tenofovir disoproxil may be considered during pregnancy, if necessary.
Safety in lactation	Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore emtricitabine/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 emtricitabine and tenofovir disoproxil in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long-term safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in patients with renal impairment emtricitabine and tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks.

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.

Emtricitabine / Tenofovir disoproxil Stada 200 mg/245 mg film-coated tablets has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex 10. How these 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 risk:

Kidney toxicity (renal toxicity)

Risk minimisation measure(s): Educational material for healthcare professionals, including renal educational brochure and a creatinine clearance slide ruler
Objective and rationale: Managing risk through medical educational activities, primarily aimed at communicating the importance of assessing creatinine clearance (CLcr) at baseline and during therapy, and the need for appropriate dose reduction in patients with renal impairment.
Summary description of main additional risk minimisation measures: • Educational material for healthcare professionals, including renal educational brochure and a creatinine clearance slide ruler Full details on these conditions and the key elements of any educational material can be found in Annex 10.

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.