**Tenofovir disoproxil STADA 245 mg film-coated tablets**

**9.3.2016, Version 1.2**

**PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN**

## *VI.2 Elements for a public summary*

### *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.[1]

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.[1]

Hepatitis B infection

Hepatitis B infection is a worldwide healthcare problem, especially in developing areas. The hepatitis B virus (HBV) is commonly transmitted via body fluids such as blood, semen, and vaginal secretions.[2]

Globally, chronic HBV infection affects 350-400 million people,[3] with disease prevalence varying among geographic regions, from 1-20%. A higher rate exists, for example, among Alaskan Eskimos, Asian Pacific islanders, Australian aborigines, and populations from the Indian subcontinent, sub-Saharan Africa, and Central Asia. In some locations, such as Vietnam, the rate is as high as 30%. Such variation is related to differences in the mode of transmission, including iatrogenic transmission, and the patient's age at infection.

The lifetime risk of HBV infection is less than 20% in low prevalence areas (< 2%; generally, 0.1-2%), and sexual transmission and percutaneous transmission during adulthood are the main modes through which it spreads. About 12% of HBV-infected individuals live in low-prevalence areas, which include the United States, Canada, western Europe, Australia, and New Zealand.[4]

### *VI.2.2 Summary of treatment benefits*

HIV-1 infection

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.[5]

This agent inhibits the activity of HIV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. It is administered as the prodrug bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir, which is converted, through various enzymatic processes, to tenofovir, a nucleotide analog of adenosine 5'-monophosphate. Bioavailability is enhanced by a high-fat meal. Prolonged intracellular distribution allows for once-daily dosing.

This drug has shown substantial efficacy and safety in PReP trials with IV drug users and heterosexually active adults. CDC guidelines recommend tenofovir alone as an alternative regimen to emtricitabine/tenofovir for these populations, but not for MSM, among whom its efficacy has not been studied.

Hepatitis B infection

The primary treatment goals for patients with hepatitis B (HBV) infection are to prevent progression of the disease, particularly to cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[6]

Tenofovir may be used as first-line therapy for treatment-naïve patients.[7] This agent is preferred as additional therapy in patients with resistance to 3TC, telbivudine, or entecavir. Tenofovir provides more potent antiviral therapy than adefovir, and it can be used as a substitute in patients who do not have an adequate response to adefovir.

### *VI.2.3 Unknowns relating to treatment benefits*

The safety and efficacy of tenofovir disoproxil in HIV-1 infected children under 2 years of age have not been established. No data are available. The safety and efficacy of tenofovir disoproxil in children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg have not been established. No data are available.

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 tenofovir disoproxil.

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil. Animal studies do not indicate reproductive toxicity. The use of tenofovir disoproxil may be considered during pregnancy, if necessary.

Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore tenofovir disoproxil should not be used during breast-feeding.

As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.

Pharmacokinetics have not been specifically studied in different ethnic groups.

There are limited data on the safety and efficacy of tenofovir disoproxil in adult 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 adult patients with renal impairment tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks.

There are limited data on the safety and efficacy of tenofovir disoproxil in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Finally, safety and efficacy data are very limited in liver transplant patients.

### VI.2.4 Summary of safety concerns

| **Important identified risks** | | |
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| **Risk** | **What is known** | **Preventability** |
| **Renal toxicity** | Tenofovir is principally eliminated via the kidney. 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. | Close monitoring of renal function is recommended in adult patients with renal impairment treated with tenofovir. The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment.<br>A multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate |

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| | | monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation. |
| **Bone events due to proximal renal tubulopathy/loss of bone mineral density** | Tenofovir may cause a reduction in BMD. The effects of tenofovir disoproxil - associated changes in BMD on long-term bone health and future fracture risk are currently unknown.<br><br>Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. | If bone abnormalities are detected or suspected, consultation with an endocrinologist and/or nephrologist should be obtained. |
| **Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients** | Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. | Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. 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.<br><br>If there is evidence of worsening liver disease in HIV/HBV co-infected patients, interruption or discontinuation of treatment must |

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| | | be considered. |
| **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.<br><br>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 several tested combinations for the treatment of HIV-1 infection. | Co-administration of tenofovir disoproxil and didanosine is not recommended. |
| **Pancreatitis** | Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. | Not known |
| **Lactic acidosis and severe hepatomegaly with steatosis** | The following side effects may be signs of lactic acidosis: | Co-administration of tenofovir and didanosine is not recommended. |

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| | o deep, rapid breathing<br>o drowsiness<br>o feeling sick (nausea), being sick (vomiting) and stomach pain | The doctor will carefully consider whether patients should be treated with the with combinations of tenofovir and didanosine<br>The doctor should be contacted immediately in case lactic acidosis is suspected. |

**Important potential risks**

| Risk | What is known (Including reason why it is considered a potential risk) |
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| **<u>Development of resistance during long-term exposure in HBV infected patients</u>** | Strains of HIV-1 with reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected in vitro and in some patients. Tenofovir disoproxil should be avoided in antiretroviral-experienced patients with strains harbouring the K65R mutation.<br>Clinical studies in treatment-experienced patients have assessed the anti-HIV activity of tenofovir disoproxil 245 mg against strains of HIV-1 with resistance to nucleoside inhibitors. The results indicate that patients whose HIV expressed 3 or more thymidine-analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced response to tenofovir disoproxil 245 mg therapy. |

**Missing information**

| Risk | What is known |
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| **<u>Safety in children (including long-term safety)</u>** | The safety and efficacy of tenofovir disoproxil in HIV-1 infected children under 2 years of age have not been established. No data are available.<br>The safety and efficacy of tenofovir disoproxil in children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg have not been established. No data are available. |

| Risk | What is known |
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| **Safety in elderly patients** | 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 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 tenofovir disoproxil. Animal studies do not indicate reproductive toxicity. The use of tenofovir disoproxil may be considered during pregnancy, if necessary. |
| **Safety in lactation** | Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore tenofovir disoproxil should not be used during breast-feeding.<br>As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant. |
| **Safety in black HBV infected patients** | Pharmacokinetics have not been specifically studied in different ethnic groups. |
| **Safety in patients with renal impairment** | There are limited data on the safety and efficacy of tenofovir disoproxil in adult 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 adult patients with renal impairment tenofovir disoproxil should only be used if the potential benefits of treatment are considered to outweigh the potential risks. |
| **Safety in patients with decompensated liver diseases and CPT score>9 (including long term safety)** | There are limited data on the safety and efficacy of tenofovir disoproxil in HBV infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary |

| Risk | What is known |
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| | and renal parameters should be closely monitored in this patient population. |
| **Safety in liver transplant recipients** | Safety and efficacy data are very limited in liver transplant patients. |

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

The SmPC for tenofovir disoproxil succinate 245 mg film-coated tablets provides physicians, pharmacists and other healthcare 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 the SmPC and PL are known as routine risk minimisation measures.Tenofovir disoproxil succinate 245 mg film-coated tablets for oral use 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 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 risk:

**Renal toxicity**

| **Safety concern 16: Renal toxicity** |
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| **Risk minimisation measure(s): Educational initiatives** |
| Objective and rationale:<br>Managing risk through medical education 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:<br>Physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:<br>– HIV renal educational brochure, including the creatinine clearance slide ruler<br>– HBV renal educational brochure, including the creatinine clearance slide ruler<br>– HIV paediatric educational brochure<br>– HBV paediatric educational brochure<br><br>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