PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

TENOFOVIR DISOPROXILORION 245 MG FILM-COATED TABLETS

ORION CORPORATION

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VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Tenofovir disoproxil fumarate is used to treat patients with human immunodeficiency virus type 1 (HIV 1) in combination with other HIV medicines. It is also used to treat chronic (long-term) hepatitis B virus infection.

HIV infection
HIV virus causes acquired immune deficiency syndrome (AIDS). AIDS is a chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV).

HIV viral infection can be transmitted through sexual contact, through blood or from mother to child during pregnancy, childbirth or breast-feeding.

According to the WHO, more than 70 million people have been infected with the HIV virus since the beginning of the epidemic and about 35 million people have died of HIV. Globally, 36.7 million [34.0–39.8 million] people were living with HIV at the end of 2015. An estimated 0.8% [0.7-0.9%] of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 25 adults (4.4%) living with HIV and accounting for nearly 70% of the people living with HIV worldwide.

Hepatitis B virus infection
Hepatitis B virus infection is a potentially life-threatening liver infection caused by the hepatitis B virus. The virus is passed from person to person through blood, semen or other body fluids.
It can cause chronic infection and puts people at high risk of serious liver diseases (cirrhosis and cancer).

According to the WHO hepatitis B prevalence is highest in sub-Saharan Africa and East Asia, where between 5–10% of the adult population is chronically infected. High rates of chronic infections are also found in the Amazon and the southern parts of eastern and central Europe. In the Middle East and the Indian subcontinent, an estimated 2–5% of the general population is chronically infected. Less than 1% of the population of Western Europe and North America is chronically infected.

VI.2.2 Summary of treatment benefits

Tenofovir belongs to a group of medicines called nucleotide reverse-transcriptase inhibitors (NRTI). Reverse transcriptase enzyme is produced by HIV. Enzyme allows HIV to infect cells and make more viruses. Tenofovir blocks the activity of reverse transcriptase.When taken in combination with other antiviral medicines, tenofovir reduces the amount of HIV in the blood and keeps it at a low level. It does not cure HIV infection or AIDS, but it may delay the damage to the immune system and the development of infections and diseases associated with AIDS.

Tenofovir also interferes with the action of an enzyme produced by the hepatitis-B virus called DNA polymerase, which is involved in the formation of viral DNA. Tenofovir stops the virus making DNA and prevents it from multiplying and spreading. It will not cure HBV, but may decrease the risk of serious liver disease developing later in life and makes it possible for the liver to repair some of the damage and to work better.

VI.2.3 Unknowns relating to treatment benefits

There is either no or only limited data regarding treatment benefits in following patient groups:

- HIV-1 infected children under 2 years of age
- children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg
- patients over the age of 65
- patients with liver transplant.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Adverse kidney effects (Renal toxicity)	In patients receiving tenofovir, rare events of reduced or insufficient kidney function and other adverse kidney effects sometimes leading to bone abnormalities have been reported.	Patient should inform doctor of any current or past kidney problems and concomitant medications before treatment is started. Use of tenofovir should be avoided with concurrent or recent use of a medicine that can have adverse effects on kidneys. Given that tacrolimus can affect kidney function, close monitoring is recommended when tacrolimus is co-administered with tenofovir. Patient's kidney function should be monitored before and during treatment in order to detect adverse effects early. If abnormalities in kidney function are suspected or detected then consultation with a kidney specialist should be obtained to consider interruption of tenofovir treatment. Interrupting treatment should also be considered in case of progressive decline of kidney function when no other cause has been identified. Stopping of the treatment usually resolves adverse effects or improves condition. However, patients with advanced HIV

Risk	What is known	Preventability
		disease, patients receiving concomitantly other medicines which have adverse effects on kidneys are at increased risk of experiencing incomplete recovery of kidney function despite of tenofovir discontinuation.
Adverse bone effects due to kidney problems/loss of bone mineral density (Bone events due to proximal renal tubulopathy/loss of bone mineral density)	Bone abnormalities (infrequently contributing to fractures) may be associated with kidney problems. Tenofovir may cause a reduction in bone mineral density (BMD). The effects of tenofovir associated changes in BMD on long-term bone health and future fracture risk are currently unknown. Findings in the animal studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.	Multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation. Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures. If bone abnormalities are detected or suspected, consultation with a medical specialist (endocrinologist and/or nephrologist) should be obtained.
Sudden temporary worsening of liver disorders in patients with HBV infection after treatment has been discontinued (Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients)	Acute exacerbation of liver inflammation (hepatitis) has been reported in patients who have discontinued hepatitis B therapy. In majority of the cases temporary worsening of the condition appears to be self-limited. However, severe exacerbations, including cases leading to death, 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.
Interaction with didanosine	Co-administration of tenofovir and didanosine results in a 40-60% increase in didanosine concentration in body that may increase the risk of didanosine-related adverse reactions.	Co-administration of tenofovir and didanosine is not recommended.

Risk	What is known	Preventability
	Co-administration also increases risk for development of resistance and treatment failure in HIV1-infected patients.	
Inflammation of pancreas (Pancreatitis)	Rarely pancreatitis, sometimes leading to death, has been reported when didanosine has been co-administered with tenofovir disoproxil fumarate. Pancreatitis is listed as possible adverse drug reaction of tenofovir therapy.	Co-administration of tenofovir and didanosine is not recommended. Doctor should be contacted immediately if symptoms of pancreatitis appear. Symptoms include e.g.: abdominal pain, nausea, vomiting, tenderness when touching the abdomen, losing weight without trying and oily, smelly stools (steatorrhea).

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Development of resistance during long-term exposure in HBV infected patients	Hepatitis B virus may develop resistance to tenofovir in long-term treatment. If resistance develops tenofovir is no longer effective against hepatitis B virus.

Missing information

Risk	What is known
Safety in children (including long-term safety)	Other formulationsof tenofovir for the treatment of HIV-1 infection and chronic hepatitis B in adolescents aged 12 to < 18 years can be available for whom a tablet form is not appropriate. The safety and efficacy of tenofovir has not been established in: • HIV-1 infected children under 2 years of age children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg. The use of tenofovir is not recommended in paediatric patients with impaired kidney function.
Safety in pregnancy	A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or adverse effects on foetus/newborn baby. Animal studies do not indicate reproductive toxicity. The use of tenofovir may be considered during pregnancy, if necessary.
Safety in lactation	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. Tenofovir has been shown to be excreted in human milk. There is

Risk	What is known
	insufficient information on the effects of tenofovir in newborns/infants. Therefore Tenofovir Orion should not be used during breast-feeding.
Safety in patients with reduced kidney function (renal impairment)	There are limited data on the safety and efficacy of tenofovir in adult patients with moderate and severe kidney impairment and long-term safety data has not been evaluated for mild kidney impairment. Therefore, in adult patients with renal impairment tenofovir should only be used if the potential benefits of treatment are considered to outweigh the potential risks. In patients with severe renal impairment and in patients who require haemodialysis use of tenofovir is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored. The use of tenofovir is not recommended in children with kidney impairment. It should not be initiated in children with kidney impairment and should be discontinued in children who develop kidney impairment during tenofovir therapy. Close monitoring of kidney function is recommended in adult patients with kidney impairment treated with tenofovir.
Safety in elderly patients	No data are available on which to make a dose recommendation for patients over the age of 65 years. Tenofovir has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased kidney function; therefore caution should be exercised when treating elderly patients with tenofovir.
Safety in black HBV infected patients	Pharmacokinetics have not been specifically studied in different ethnic groups.
Safety in HBV infected patients with severe advanced liver disease, including long-term safety [Safety in HBV infected patients with decompensated liver disease and CPT score > 9 (including long-term safety)]	There are limited data on the safety and efficacy of tenofovir in HBV infected patients with severe advanced liver disease. These patients may be at higher risk of experiencing serious liver or kidney adverse reactions. Therefore, liver, bile and kidney parameters should be closely monitored in this patient population. Liver flares (sudden temporary worsening of the liver disease) are especially serious, and sometimes leading to death in patients with severe advanced liver disease.
Safety in liver transplant recipients infected with hepatitis B virus	Safety and efficacy data are very limited in liver transplant patients.

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 package leaflet (PL). The measures in these documents are known as routine risk minimisation measures. The Summary of Product Characteristics and the Package leaflet for this medicinal product can be found in the national authority's web page.

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

These additional risk minimisation measures are for the following risks:

Adverse kidney effects (Renal toxicity)

Risk minimisation measures: Educational materials
Objective and rationale: 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: • HIV renal educational brochure for prescribers of adult patients • HIV renal educational brochure for prescribers of pediatric patients • HBV renal educational brochure for prescribers of adult patients • HBV renal educational brochure for prescribers of pediatric patients

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

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

Not applicable.