This Educational Material contains important safety information about **Tenofovir disoproxil Mylan 245mg** and advice on risk minimisation.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Medicines Authority at http://www.medicinesauthority.gov.mt/adrportal or to the local representative of Mylan S.A.S. : V.J. Salomone Pharma Ltd., Upper Cross Road, Marsa MRS1542, Malta, Tel: +356 21 220 174 and 24h PV mobile +356 99644126

This brochure provides important advice on the management of potential renal and bone effects of tenofovir in HIV-1 and chronic HBV infected children and adolescents aged 12 to <18 years, and on the dosing recommendations for tenofovir in this population

Important points to consider

- ✓ A multidisciplinary approach is recommended for the management of children and adolescents
- ✓ There is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil fumarate-containing products
- ✓ Check all patients' creatinine clearance and serum phosphate before starting tenofovir therapy
- ✓ During tenofovir therapy, renal function (creatinine clearance and serum phosphate) should be assessed regularly (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) (see Table 1)
- ✓ In patients at risk for renal impairment a more frequent monitoring of renal function is required
- ✓ Tenofovir is not recommended for use in patients aged 12 to < 18 years with renal impairment
- ✓ Re-evaluate renal function within 1 week if serum phosphate is confirmed to be <3.0 mg/dL (0.96 mmol/L) during tenofovir therapy in any patient aged 12 to < 18 years
- ✓ If renal abnormalities are suspected or detected consult with a nephrologist to consider interrupting tenofovir therapy. Also consider interrupting treatment with tenofovir in case of progressive decline of renal function when no other cause has been identified
- ✓ Avoid concurrent or recent use of nephrotoxic medicinal products

- ✓ 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 in children and adolescents
- ✓ If bone abnormalities are suspected or detected, consult with an endocrinologist and/or a nephrologist

Management of renal effects

There are uncertainties associated with the long-term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a 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.

In clinical studies and post-marketing safety surveillance of tenofovir in adults, events of renal failure, renal impairment, and proximal renal tubulopathy (including Fanconi syndrome) have been reported. In some patients proximal renal tubulopathy has been associated with myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures), rhabdomyolysis, muscle weakness, hypokalaemia and hypophosphataemia.

Tenofovir is not recommended for use in children or adolescents with renal impairment. Tenofovir should not be initiated in children or adolescents with renal impairment and should be discontinued in children or adolescents who develop renal impairment during tenofovir therapy.

The recommendations for monitoring renal function in children and adolescent patients without renal risk factors prior to and during tenofovir therapy are provided in Table 1 below. In patients at risk for renal impairment a more frequent monitoring of renal function is required.

Table 1: Monitoring of renal function in patients without renal risk factors

	Prior to tenofovir	**During 1st 3 months on tenofovir**	**>3 months on tenofovir**
Frequency	At baseline	At 2 to 4 weeks and 3 months	Every 3 to 6 months
Parameter	Creatinine clearance and serum phosphate	Creatinine clearance and serum phosphate	Creatinine clearance and serum phosphate

- ✓ If serum phosphate is confirmed to be <3.0 mg/dL (0.96 mmol/L), renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. If renal abnormalities are suspected or detected consult with a

nephrologist to consider interrupting tenofovir therapy. Also consider interrupting treatment with tenofovir in case of progressive decline of renal function when no other cause has been identified

Use of tenofovir should be avoided with concurrent or recent use of a nephrotoxic medicinal product and drugs secreted by the same pathway; if concomitant use is unavoidable, renal function should be monitored weekly.

A higher risk of renal impairment has been reported in patients receiving tenofovir in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients. In patients with renal risk factors, the co-administration of tenofovir with a boosted protease inhibitor should be carefully evaluated.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir and with risk factors for renal dysfunction. If tenofovir is co-administered with an NSAID, renal function should be monitored adequately.

Management of bone effects

Tenofovir may cause a reduction in BMD. Reductions in BMD have been reported in paediatric patients. In adolescents, the BMD Z-scores at 48 weeks observed in subjects who received tenofovir were lower than those observed in subjects who received placebo. In children, the BMD Z-scores observed at 48 weeks in subjects who switched to tenofovir were lower than those observed in subjects who remained on their stavudine or zidovudine-containing regimen. The effects of tenofovir associated changes in BMD on long term bone health and future fracture risk are currently unknown in patients aged 12 to < 18 years.

If bone abnormalities are suspected or detected, then consultation with an endocrinologist and/or a nephrologist should be obtained.

Dosing recommendations for tenofovir in Children and Adolescents

HIV-1/chronic hepatitis B: In adolescents aged 12 to < 18 years and weighing ≥ 35 kg, the recommended dose of tenofovir disoproxil is 245 mg (one tablet) once daily taken orally with food.

Reduced doses of tenofovir disoproxil are used for treatment of HIV-1 infected paediatric patients aged 2 to < 12 years. As Tenofovir disoproxil Mylan is available only as 245 mg film-coated tablets, it is not suitable for the use in paediatric patients aged 2 to < 12 years.

Tenofovir disoproxil 245 mg film-coated tablets are approved for the treatment of chronic hepatitis B in adolescents aged 12 to <18 years of age and weighing ≥ 35 kg with compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently

elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis. No data are currently available in children with chronic hepatitis B aged 2 to < 12 years or weighing <35 kg.

For treatment of HIV-1 infection or chronic hepatitis B in adolescents aged 12 to <18 years for whom a solid dosage form is not appropriate, other suitable formulations should be checked for their availability.