Renal monitoring tool (paediatric patients)

This brochure provides important advice on the management of potential renal and bone effects of tenofovir disoproxil. Emtricitabine/tenofovir disoproxil is indicated for the treatment of HIV-1 infected adolescents aged 12 to <18 years, with NRTI resistance or toxicities precluding the use of first-line agents. Adolescents aged 12 years and older, weighing at least 35 kg, should take one tablet, once daily. The safety and efficacy of emtricitabine/tenofovir disoproxil in children under the age of 12 years have not been established.

Important points to consider

- ✓ A multidisciplinary approach is recommended for the management of children and adolescents
- ✓ Check all patients' creatinine clearance and serum phosphate before starting tenofovir disoproxil therapy
- ✓ During tenofovir disoproxil 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 disoproxil should not be used in children or adolescents 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 disoproxil therapy
- ✓ If renal abnormalities are suspected or detected consult with a nephrologist to consider interrupting tenofovir disoproxil therapy. Also consider interrupting treatment with tenofovir disoproxil 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 disoproxil 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 in children and adolescents
- ✓ If bone abnormalities are suspected or detected, consult with an endocrinologist and/ or a nephrologist.
- ✓ There is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil containing products.

Management of renal effects

There are uncertainties associated with the long-term effects of tenofovir disoproxil bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to weigh adequately 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 disoproxil 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 hypophosphatemia.

Tenofovir disoproxil is not recommended for use in children or adolescents with renal impairment. Tenofovir disoproxil 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 disoproxil therapy.

The recommendations for monitoring renal function in children and adolescent patients without renal risk factors prior to and during tenofovir disoproxil therapy are provided in Table 1. 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 disoproxil	**During 1st 3 months on tenofovir disoproxil**	**>3 months on tenofovir disoproxil**
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 then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil treatment. Also consider interrupting treatment with tenofovir disoproxil in case of progressive decline of renal function when no other cause has been identified. Use of tenofovir disoproxil 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 disoproxil 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 disoproxil 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 disoproxil and with risk factors for renal dysfunction. If tenofovir disoproxil is co-administered with an NSAID, renal function should be monitored adequately.

Management of bone effects
Tenofovir disoproxil 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 disoproxil 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 disoproxil were lower than those observed in subjects who remained on their stavudine or zidovudine-containing regimen.

The effects of tenofovir disoproxil associated changes in BMD on long term bone health and future fracture risk are currently unknown.

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

Dosing recommendations for tenofovir disoproxil in Children and Adolescents
Tenofovir disoproxil available formulations for use in children and adolescents aged 2 to <18 years and emtricitabine/tenofovir disoproxil available formulations for use in adolescents aged 12 to <18 years.

The following formulations of emtricitabine/tenofovir disoproxil are available for use in children and adolescents depending on age and weight:

Age (year (s)	Body Weight (kg)	Tenofovir disoproxil Formulation (Once Daily)	Emtricitabine/tenofovir disoproxil Formulation (Once Daily)*
12 to <18	≥35	245 mg tablet	200 mg/245 mg tablets
6 to <12	28 to <35	204 mg tablet	Not approved in children less than 12 years
6 to <12	22 to <28	163 mg tablet	
6 to <12	17 to <22	123 mg tablet	
2 to <18	≥10	33 mg/granules	

*Separate preparations of emtricitabine and tenofovir disoproxil fumarate are available for treatment of HIV-1 infection if it becomes necessary to discontinue or modify the dose of one of the components of emtricitabine/tenofovir disoproxil formulation. Please refer to the Summary of Product Characterstics for these medicinal products.

Dosing recommendations for tenofovir disoproxil 33 mg/g granules for use in paediatric patients
The recommended dose of tenofovir disoproxil 33 mg/g granules is 6.5 mg of tenofovir disoproxil (as fumarate) per kilogram of body weight. Limited clinical data are available at the 6.5 mg/kg dose of the granules. Therefore, close monitoring of efficacy and safety is needed.

Dosing recommendations for tenofovir disoproxil 33 mg/g granules for use in children and adolescents aged 2 to < 18 years
Dosing recommendations for tenofovir disoproxil 33 mg/g granules for use in children and adolescents aged 2 to < 18 years are as follows:

Body Weight (kg)	Once Daily Scoops of Granules
10 to <12	2
12 to <14	2.5
14 to <17	3
17 to <19	3.5
19 to <22	4
22 to <24	4.5
24 to <27	5
27 to <29	5.5
29 to <32	6
32 to <34	6.5
34 to <35	7
≥35	7.5

Please report any adverse events suspected to be caused by the use of Emtricitabine/Tenofovir Disoproxil Rowex to Rowex Ltd, Bantry, Co Cork. Tel 027 50077; fax 027 50417 or the HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie