**This brochure provides important advice on the management of potential renal and bone effects of tenofovir disoproxil (TD) in HIV-1 infected children and adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to <18 years, and on the dosing recommendations for TD in this population.**

## 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 TD therapy
- ✓ During TD 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
- ✓ TD 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 TD therapy
- ✓ If renal abnormalities are suspected or detected consult with a nephrologist to consider interrupting TD therapy. Also consider interrupting treatment with TD in case of progressive decline of renal function when no other cause has been identified
- ✓ Avoid concurrent or recent use of nephrotoxic medicinal products
- ✓ TD may cause a reduction in bone mineral density (BMD). The effects of TD 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 TD 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.

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

The recommendations for monitoring renal function in children and adolescent patients without renal risk factors prior to and during TD 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 TD** | **During first 3 months on TD** | **>3 months on TD** |
|---|---|---|---|
| **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 TD treatment. Also consider interrupting treatment with TD in case of progressive decline of renal function when no other cause has been identified.

Use of TD 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 TD 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 TD 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 TD and with risk factors for renal dysfunction. If TD is co-administered with an NSAID, renal function should be monitored adequately.

## Management of Bone Effects

TD 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 TD 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 TD were lower than those observed in subjects who remained on their stavudine or zidovudine-containing regimen. The effects of TD 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 TD in Children and Adolescents

Emtricitabine/Tenofovir disoproxil Krka is approved for the treatment of HIV-1 infected children and adolescents aged 12 to < 18 years, with NRTI resistance or toxicities precluding the use of first line agents.
The following formulation of Emtricitabine/Tenofovir disoproxil Krka is available for use in children and adolescents depending on age and weight:

| **Age (years)** | **Body Weight (kg)** | **TD Formulation (Once Daily)** |
|---|---|---|
| 12 to <18 | ≥35 | 245 mg tablet |

*Refer to the latest SmPC for prescribing information available at https://www.ema.europa.eu/en/documents/product-information/emtricitabine/tenofovir-disoproxil-krka-dd-epar-product-information_en.pdf

## Reporting of Side Effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the patient information leaflet. You can also report side effects directly via the national reporting system: *HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +3531 6764971; Fax: +3531 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie*
Any suspected adverse reactions can also be reported to Krka, d. d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto; Tel: +386 7 331 21 11 and +386 1 47 51 100; Website: www.krka.si; Email: pharmacovigilance@krka.biz.
When reporting a suspected adverse reaction, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

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# Advice for Healthcare Professionals on the Use of Tenofovir Disoproxil (TD) for the Treatment of HIV-1 Infected Children and Adolescents

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