Management of bone effects

Tenofovir disoproxil may cause a reduction in BMD. Reductions in BMD have been reported in adolescent patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed 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 detected or suspected in adolescent patients, consultation with an endocrinologist and/or nephrologist should be obtained.

Any suspected adverse reactions to Tenofovir disoproxil Teva or Emtricitabine/Tenofovir disoproxil Teva should be reported to Teva via email to safety.ireland@teva.ie or by telephone to +442075407117.

You can also report side effects directly via the national reporting system: HPRA Pharmacovigilance, Earlsfort Terrace, Dublin, Ireland.
Tel +353 1 6764971; Fax +353 1 6762517;
Email: medsafety@hpra.ie; Website: www.hpra.ie

REFERENCES
1. Summary of Product Characteristics for Tenofovir Disoproxil Teva 245 mg Film-coated Tablets
2. Summary of Product Characteristics for Emtricitabine/Tenofovir disoproxil Teva 200mg/245mg Film-coated Tablets.

Date of Preparation: January 2019. IE/GEN/17/0015d(1).

Digital Office Centre Swords, Suite 101 - 103, Balheary Demense,
Balheary Road, Swords, Co Dublin, K67E5AO, Ireland.
Freephone: 1800 201 7000 | Tel: +353 51 321 740 | Fax: +353 (0)42 935 1516

Ireland
Teva Pharmaceuticals Ireland
www.teva.ie

Treatment of adolescent patients with HIV

Recommendations relating to Renal Management and dose adjustment for Healthcare Professionals with adolescent patients receiving medication containing tenofovir disoproxil for HIV

Important points to consider

HIV-positive patients are at risk of renal disease in connection with the use of products containing tenofovir disoproxil. There are uncertainties associated with the long-term effects of bone and renal toxicity in adolescent patients. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended for the management of adolescent patients in order to adequately weigh the benefit/risk balance of treatment on a case by case basis, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation. Special recommendations relating to adolescent patients being treated with regimens based on tenofovir disoproxil are set out below:

- Check all patients' creatinine clearance and serum phosphate before starting tenofovir disoproxil therapy.
- During tenofovir disoproxil therapy, renal function (creatinine clearance and serum phosphate) must be regularly monitored during treatment (after 2 to 4 weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors) *(see Table 1 overleaf).*
- In patients at risk of renal impairment a more frequent monitoring of the kidney function is required.
- Tenofovir disoproxil is not recommended for use in adolescent patients with renal impairment. Tenofovir disoproxil should not be initiated in adolescent patients with renal impairment and should be discontinued in adolescent patients who develop renal impairment during tenofovir disoproxil therapy.
- 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.
- If bone abnormalities are suspected or detected in adolescent patients, consultation with an endocrinologist and/or nephrologist should be obtained.

Management of Renal Effects

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 hypophosphataemia.

The recommendations for monitoring the renal function in all patients before and during treatment with tenofovir disoproxil are set out in table 1 below:

Table 1: Renal function monitoring[1,2]

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

* In patients at risk for renal impairment a more frequent monitoring of renal function is required

If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any adolescent patient receiving tenofovir disoproxil, 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.

Interrupting treatment with tenofovir disoproxil should also be considered 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 eliminated by the same route. If concomitant use of tenofovir disoproxil and nephrotoxic agents is unavoidable, renal function should be monitored weekly[1,2].

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.

Dosing recommendations for tenofovir disoproxil in adolescents

Tenofovir disproxil Teva and Emtricitabine/Tenofovir disoproxil Teva are approved for the treatment of HIV-1 infected adolescents with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to <18 years. The safety and efficacy of tenofovir disoproxil in HIV-1 infected children under 2 years of age have not been established. No data is available.

Table 2: Dosing recommendations for tenofovir disoproxil in adolescents and children

Age (years)	Body weight (kg)	Tenofovir disoproxil Teva	Emtricitabine/ Tenofovir disoproxil Teva
12 to <18	≥35kg	245 mg tablet once daily	200 mg/245 mg tablet once daily
2 to <12 years	<35 kg	Tenofovir disoproxil Teva is available only as 245 mg film-coated tablets, therefore it is not suitable for use in paediatric patients aged 2 to <12 years. Other suitable formulations may be checked for their availability	Not approved in children less than 12 years