Emtricitabine/ Tenofovir disoproxil Mylan HIV Paediatric Renal Educational Guide for prescribers, Global Version v. 2.1/01Nov2021

This EM contains important safety information about Invented name (**Emtricitabine/Tenofovir disoproxil Mylan**) and advice on risk minimisation.

This booklet was developed by MAH.

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 Medicines Authority at http://www.medicinesauthority.gov.mt/adrportal
Adverse reactions/events should also be reported to MAH at e-mail address or to the local representative of Viatris : V.J. Salomone Pharma Ltd., Upper Cross Road, Marsa MRS1542, Malta, Tel:+356 21 220 174 and 24h PV mobile +356 99644126

This guide provides important advice on the management of potential renal and bone effects of tenofovir

Therapeutic Indication of Emtricitabine/tenofovir disoproxil Mylan in paediatric patients Emtricitabine/tenofovir disoproxil Mylan fixed-dose combination tablet is approved, in combination with other antiretroviral medicinal products, 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 Emtricitabine/tenofovir disoproxil Mylan tablet, once daily. The safety and efficacy of Emtricitabine/tenofovir disoproxil Mylan in childrenunder 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 Emtricitabine/tenofovir disoproxil Mylan therapy
- During Emtricitabine/tenofovir disoproxil Mylan therapy, renal function (creatinine clearance and serum phosphate) should be assessed regularly (after two to four weeksof treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors) (see Table 1). In individuals atrisk of renal disease, more frequent monitoring of renal function is required
- In patients at risk for renal impairment or of renal disease, a more frequent monitoring of renal function is required

- Tenofovir is not recommended for use 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 therapy
- 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 uncertain 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 TDF containing products

Management of renal effects

There are uncertainties associated with the long-term effects of tenofovir-associated 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 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), renalfunction should be reevaluated 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 treatment. 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. 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 uncertain.

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

Treatment of HIV in adults and adolescents aged 12 years and older, weighing at least 35 kg: One tablet, once daily.

Prevention of HIV in adults and adolescents aged 12 years and older, weighingat least35 kg: One tablet, once daily.

Reduced doses of tenofovir disoproxil are used for treatment of HIV-1 infected paediatric patients aged 2 to < 12 years. As Emtricitabine/tenofovir disoproxil Mylan is available only as 200/245 mg film-coated tablets, it is not suitable for the use in paediatric patients aged 2 to < 12 years. For treatment of HIV-1 infection in adolescents aged 12 to <18 years for whom a solid dosage form is not appropriate, other suitable formulations may be checked for their availability.

Local version 1.0

NCA approval date 09-FEB-2022

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