Recommendations on Use of Tenofovir Disoproxil in the Treatment of Adolescents With Chronic Hepatitis B and/or Infected with HIV-1

Reporting of adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicinal product is important as it allows continuous monitoring of the benefit-risk balance of the medicinal product. Report any suspected adverse reactions using the following contacts:

You can report side effects directly using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;

Post: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings,
Malta Life Sciences Park, San Ġwann SĠN 3000
E-mail: postlicensing.medicinesauthority@gov.mt

Alternatively, they may be reported by contacting local representative V.J. Salomone Pharma Ltd. at +35699644126.

Recommendations on Bone Risk Management and Renal Monitoring in Adolescents With Chronic Hepatitis B and/or HIV-1 Infected Adolescents Taking Tenofovir Disoproxil and Dosage in this Population

In adolescent patients with chronic hepatitis B and/or infected with HIV-1, there is an increased risk of kidney disease associated with the use of medicines containing tenofovir disoproxil, such as Tenofovir Aurovitas and Tenofovir Farmoz (containing only tenofovir disoproxil) and Emtricitabine + Tenofovir Farmoz and Emtricitabine + Tenofovir Generis (containing emtricitabine + tenofovir disoproxil).

These medicines containing tenofovir disoproxil may also cause a decrease in bone mineral density (BMD).

Specific recommendations for the treatment of adolescent patients with these medicinal products are described below.

Dosage recommendations in adolescents with chronic hepatitis B

Tenofovir disoproxil is indicated for the treatment of chronic hepatitis B in adolescents aged 12 to 18 years aged and weighing >35 kg with compensated liver disease and evidence of active immune disease, i.e., active viral replication, persistently elevated serum alanine aminotransferase levels, and histological evidence of inflammation and/or fibrosis. The recommended dose is one tablet, once a day, with food.

For the treatment of chronic hepatitis B in adolescents for whom a solid dosage form is not appropriate, other suitable formulations may be available.

There are no data on safety or efficacy in children with chronic hepatitis B under 12 years of age or weighing <35 kg.

Dosing recommendations in HIV-1 infected adolescents

Tenofovir disoproxil and emtricitabine + tenofovir disoproxil are indicated for the treatment of adolescents between 12 and 18 years of age who are infected with HIV-1 with resistance to nucleoside reverse transcriptase inhibitors (NRTIs) or with toxicities that exclude the use of first-line medicines. The recommended dose is one tablet, once a day, orally, with food.

The safety and efficacy of Tenofovir Aurovitas® and Tenofovir Farmoz® in HIV-1 infected children with less than of 12 years of age or with a weight <35kg have not been established.

Important Issues to Consider

1. A multidisciplinary approach is recommended for the management of adolescent patients;
2. Check the creatinine clearance and serum phosphate of all patients prior to initiating therapy with Tenofovir disoproxil or Emtricitabine + Tenofovir disoproxil;
3. During treatment, renal function (creatinine clearance and serum phosphate) should be assessed regularly (after two to four weeks of treatment, after three months of treatment, and then at intervals of three to six months in patients without risk factors for renal disease) (see **Table 1**);
4. In patients at risk of renal impairment, more frequent monitoring of renal function is required;
5. Tenofovir disoproxil should not be used in adolescents with impaired renal function;
6. Renal function should be reassessed within one week if serum phosphate is confirmed to be <3.0 mg/dL (0.96mmol/L) during treatment with Tenofovir disoproxil;
7. If renal abnormalities are detected or suspected, consultation with a nephrologist should be sought to consider discontinuing treatment with tenofovir disoproxil. Discontinuation of treatment should also be considered in case of progressive decline in renal function in cases where no other cause has been identified;
8. Avoid concomitant or recent use of nephrotoxic drugs;
9. Tenofovir disoproxil may cause a decrease in BMD. The effects of changes in BMD associated with tenofovir disoproxil on long-term bone health and future risk of fractures are uncertain in adolescent patients;
10. If bone abnormalities are detected or suspected in adolescent patients, consultation with an endocrinologist and/or nephrologist should be sought.

Monitoring of renal function

There are uncertainties associated with the long-term effects of renal and bone toxicity. In addition, the reversibility of renal toxicity may not be fully verified. Therefore, a multidisciplinary approach is recommended to properly weigh the benefit/risk balance of treatment on a case-by-case basis, decide on appropriate monitoring during treatment (including the decision to withhold treatment) and consider the need for supplementation. In clinical studies and in the post-marketing safety surveillance of tenofovir disoproxil, 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 (manifesting as bone pain and infrequently contributing to fractures), rhabdomyolysis, muscle weakness, hypokalemia, and hypophosphatemia.

Tenofovir disoproxil should not be recommended for adolescents with renal impairment. Tenofovir disoproxil should not be initiated in adolescent patients with renal impairment and should be discontinued in patients adolescents who developed renal impairment during treatment.

Recommendations for monitoring renal function in adolescents without risk factors for renal disease, prior to and during tenofovir disoproxil therapy, are described in Table 1. In patients at risk of renal impairment, more frequent monitoring of renal function is required.

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

	Before Tenofovir Disoproxil	During the first 3 months with Tenofovir disoproxil	>3 months with Tenofovir disoproxil
Frequency	Beginning	After 2 to 4 weeks and at 3 months	At intervals of 3 to 6 months
Parameter	Serum creatinine and phosphate clearance	Serum creatinine and phosphate clearance	Serum creatinine and phosphate clearance

If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l), renal function should be reassessed within one week, including blood glucose and potassium levels and urine glucose concentrations. If renal abnormalities are detected or suspected, consultation with a nephrologist should be sought to consider discontinuing treatment with tenofovir disoproxil. Discontinuation of treatment should also be considered in case of progressive decline in renal function in cases where no other cause has been identified.

The use of tenofovir disoproxil should be avoided with recent or concomitant use of nephrotoxic medicinal products and drugs secreted by the same route; 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. In these patients, careful monitoring of renal function is required. 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 have been reported following initiation of high doses or multiple Nonsteroidal anti-inflammatory drugs (NSAIDs) 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 closely monitored.

Monitoring of bone effects

Tenofovir disoproxil may cause a reduction in BMD. Cases of decreased BMD have been reported in paediatric patients. The effects of changes in BMD associated with tenofovir disoproxil on long-term bone health and future fracture risk are uncertain in paediatric patients.

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