This brochure provides important advice on the management of potential renal and bone effects of tenofovir disoproxil fumarate (TDF) in HIV-1 infected children and adolescents aged 2 to <18 years, and on the dosing recommendations for TDF in this population.[1,2]

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 TDF therapy
- ✓ During TDF therapy, renal function (creatinine clearance and serum phosphate) should be assessed regularly (every 4 weeks during the 1st year and then every 3 months) (see Table 1 below)
- ✓ Consider more frequent monitoring of renal function in patients at risk for renal impairment
- ✓ TDF 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 TDF therapy
- ✓ If renal abnormalities are suspected or detected consult with a nephrologist to consider interrupting TDF therapy
- ✓ Avoid concurrent or recent use of nephrotoxic medicinal products
- ✓ TDF may cause a reduction in bone mineral density (BMD). The effects of TDF 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 TDF 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.

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

The recommendations for monitoring renal function in all children and adolescent patients prior to and during TDF therapy are provided in Table 1 below.

Table 1: Monitoring of renal function

	Prior to TDF	During 1st year on TDF*	>1 year on TDF*
Frequency	At baseline	Every 4 weeks	Every 3 months
Parameter	Creatinine clearance and serum phosphate	Creatinine clearance and serum phosphate	Creatinine clearance and serum phosphate

* In patients at risk for renal impairment, consideration should be given to more frequent monitoring of renal function.

Use of TDF 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.

Co-administration with lopinavir/ritonavir, atazanavir/ritonavir or darunavir/ritonavir increases tenofovir concentrations, and could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored if TDF is co-administered with these medicinal products.

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 TDF treatment.

Management of bone effects

TDF 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 TDF 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 TDF were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen.

The effects of TDF 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 TDF in Children and Adolescents

Viread is approved, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infected children and adolescents aged 2 to < 18 years, with NRTI resistance or toxicities precluding the use of first line agents. No data are currently available in HIV-1 infected children under 2 years of age.

The following formulations of Viread are available for use in children and adolescents depending on age and weight:[1,2]

Age (years)	Body Weight (kg)	TDF Formulation (Once Daily)
12 to <18	≥35	245 mg tablet
6 to <12	28 to <35	204 mg tablet
6 to <12	22 to <28	163 mg tablet
6 to <12	17 to <22	123 mg tablet
2 to <18	≥10	33 mg/g granules

The recommended dose of Viread 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.[2]

Dosing recommendations for the Viread 33 mg/g granules for HIV-1 infected children and adolescents aged 2 to < 18 years are as follows:[2]

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

VIREAD® PRESCRIBING INFORMATION

Presentation: Viread film-coated tablet containing 245mg of tenofovir disoproxil (as fumarate), equivalent to 300mg of tenofovir disoproxil fumarate, or 136mg of tenofovir. Viread is also available as 33 mg/g granules, 123 mg, 163 mg & 204 mg film-coated tablets. Please refer to the individual SPCs for indications and further information.

Indications: 1) The treatment of chronic hepatitis B (CHB), in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. 2) Treatment of CHB in adults with decompensated liver disease. 3) Treatment of CHB in adolescents 12 to < 18 years of age with compensated liver disease and evidence of immune active disease, i.e. active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis. 4) In combination with other antiretroviral medicinal products for treatment of HIV-1-infected adults. 5) Treatment of HIV-1-infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

Dosage & Administration: Adults: One tablet (245mg) once daily taken with food. Viread available as 33 mg/g granules for the treatment of CHB and HIV-1 infection in adults for whom a solid dosage form is not appropriate. Not recommended in adult patients with severe renal impairment (creatinine clearance (CrCl) <30ml/min). No dose modification necessary in patients with mild to moderate liver disease. Optimal duration of treatment is unknown. Children and adolescents: for the treatment of CHB and HIV-1 infection in adolescents aged 12 to < 18 years and weighing ≥ 35 kg, recommended dose is one tablet (245mg) once daily taken with food. The safety and efficacy of tenofovir disoproxil fumarate in children with CHB aged 2 to < 12 years or weighing < 35 kg and HIV-1-infected children under 2 years of age have not been established. Viread available as 33 mg/g granules for the treatment of CHB and HIV-1 infection in adolescents aged 12 to < 18 years for whom a solid dosage form is not appropriate and for use in HIV-1-infected paediatric patients aged 2 to < 12 years and as reduced tablet strengths for use in HIV-1-infected paediatric patients aged 6 to < 12 years. Not recommended in paediatric patients with renal impairment. No dose adjustment is required in patients with hepatic impairment.Please refer to the SPCs for Viread 33 mg/g granules & 123 mg, 163 mg & 204 mg film-coated tablets. Elderly: Insufficient data are available on which to make dose recommendations for patients over the age of 65 years – caution should be exercised.

Contraindications: Known hypersensitivity to tenofovir, tenofovir disoproxil fumarate, or any of the excipients.

Warnings and Precautions: Renal: Renal failure and impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice. It is recommended that CrCl is calculated in all patients prior to therapy initiation and renal function monitored every 4 weeks for the first year and every 3 months thereafter. In patients at risk of renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in adult patients with impaired renal function. Tenofovir disoproxil fumarate should only be used in these patients if the potential benefits outweigh the risks. For adult patients with CrCl < 50ml/min, the dosing interval should be adjusted as follows: moderate renal impairment (CrCl 30-49 ml/min) – 1 tablet every 48 hours. Severe renal impairment (CrCl < 30 ml/min) and in patients who require haemodialysis use of tenofovir disoproxil fumarate is not recommended. Refer to SPC for full monitoring and dose adjustment recommendations. Not recommended in paediatric patients with renal impairment. Tenofovir disoproxil fumarate should be discontinued in paediatric patients who develop renal impairment during therapy.

HIV Co-infection: HIV antibody testing should be offered to all HBV-infected patients before initiating tenofovir disoproxil fumarate therapy. Due to the risk of development of HIV resistance, tenofovir disoproxil fumarate should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients. Patients must be advised tenofovir disoproxil has not been proven to prevent the risk of transmission of HIV or HBV to others through sexual contact or contamination with blood and appropriate precautions must be used.

Exacerbations of hepatitis: Flares on treatment: Spontaneous exacerbations in CHB are relatively common. Patients with cirrhosis may be at higher risk for hepatic exacerbations and therefore should be monitored closely. However it also should be noted that increase in ALT can be part of HBV clearance during therapy with tenofovir. Flares after treatment discontinuation: Acute exacerbations of hepatitis have also been reported in patients who have discontinued hepatitis B therapy. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of therapy.

References

1. Summaries of Product Characteristics for VIREAD 123 mg, 163 mg, 204 mg and 245 mg film-coated tablets
2. Summary of Product Characteristics for VIREAD 33 mg/g granules

Date of Preparation: March 2013

HIV/IHQ/04-13//XXXX

Treatment discontinuation is not recommended in patients with advanced liver disease or cirrhosis, since post-treatment exacerbations of hepatitis may lead to hepatic decompensation. Co-infection with hepatitis C or D: There are no data on the efficacy of tenofovir in patients co-infected with hepatitis C or D virus. Hepatic decompensation: There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in HBV-infected patients with decompensated liver disease and who have a Child-Pugh-Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Hepatic disease: Safety and efficacy data are very limited in liver transplant patients. Other: Lactic acidosis and lipodystrophy – refer to SPC for recommendations regarding monitoring. Viread may cause a reduction in BMD. If bone abnormalities are detected/suspected in paediatric patients, consult an endocrinologist and/or nephrologist. Bone abnormalities (may be associated with proximal renal tubulopathy). Triple nucleoside/nucleotide therapy: Mitochondrial dysfunction. Immune Reactivation Syndrome. Osteonecrosis. Avoid in antiretroviral experienced patients harbouring K65R mutation.

Interactions: Low potential for CYP450 mediated interactions with other medicinal products. Viread should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate or adefovir dipivoxil, nephrotoxic agents or medicinal products that reduce renal function or compete for active tubular secretion. Monitor renal function if tenofovir disoproxil fumarate administered with tacrolimus. Co-administration with didanosine is not recommended as it may result in a 40-60% increase in systemic exposure to didanosine which may increase the risk of didanosine-related adverse events. Co-administration with 400 mg daily didanosine has been associated with significant decreases in CD4 cell counts. A reduced dose of 250 mg didanosine administered with tenofovir disoproxil fumarate has been associated with reports of high rates of virological failure. Co-administration with lopinavir/ritonavir; 30% increase in tenofovir AUC. Co-administration with atazanavir/ritonavir decreased atazanavir concentrations, but increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir associated adverse events including renal disorders. Food has been shown to enhance the bioavailability of Viread. Refer to SPC for drug interaction details for protease inhibitors, NRTIs, NNRTIs.

Use in pregnancy and lactation: The use of Viread may be considered during pregnancy. Viread should not be used during breast feeding.

Side effects: Very commonly reported adverse events (≥1/10): hypophosphataemia*, dizziness, diarrhoea, vomiting, nausea, rash, asthenia. Common (≥1/100 to <1/10): flatulence, headache, abdominal pain, abdominal distension, fatigue, increased transaminases. Uncommon (≥ 1/1,000 to < 1/100): hypokalaemia*, pancreatitis, rhabdomyolysis*, muscular weakness, increased creatinine. Rare (≥1/10,000, <1/1,000): lactic acidosis, hepatic steatosis, hepatitis, angioedema, osteomalacia*, myopathy*, renal failure, acute renal failure, proximal renal tubulopathy including Fanconi syndrome, acute tubular necrosis, nephritis, nephrogenic diabetes insipidus. The side effects marked * may occur as a consequence of proximal renal tubulopathy. In patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART), cases of osteonecrosis have been reported. Inflammatory reaction to asymptomatic or residual opportunistic infections may arise in patients with severe immunodeficiency at the time of initiation of CART. CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, hyperlactataemia and lipodystrophy. In patients with CHB, exacerbations of hepatitis during treatment may arise. Refer to SPC for full information on adverse events.

Overdosage: If overdose occurs, monitor for evidence of toxicity. Apply standard supportive treatment if necessary. Tenofovir can be removed by haemodialysis.

Pharmaceutical Precautions: No special precautions for storage or handling.

Package Quantities: Bottle of 30 film coated tablets

Marketing Authorisation numbers: EU/1/01/200/001

Further information is available from the marketing authorisation holder: Gilead Sciences International Ltd, Granta Park, Abington, Cambridge CB21 6GT.

Telephone: + 44 (0) 1223897555. Email: ukmedinfo@gilead.com

CONSULT THE SUMMARY OF PRODUCT CHARACTERISTICS BEFORE PRESCRIBING PARTICULARLY IN RELATION TO SIDE EFFECTS, PRECAUTIONS AND CONTRAINDICATIONS.

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Suspected adverse drug reactions (ADRs) should be reported to the Medicines Authority Post-Licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA or at http:/www.medicinesauthority.gov.mt/pub/adr.doc

Suspected adverse drug reactions may also be reported to GILEAD SCIENCES INTERNATIONAL LTD via email to csafety@gilead.com or tel: +44 (0) 1223 897500 or to AM MANGION Ltd via email to pv@ammangion.com.mt or tel: (+356) 2397 6333

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

GILEAD

Prescribing information can be found on the back.