ADVICE FOR HEALTHCARE PROFESSIONALS ON THE USE OF TENOFOVIR DISOPROXIL FUMARATE (TDF) FOR THE TREATMENT OF CHRONIC HEPATITIS B IN CHILDREN AND ADOLESCENTS

This brochure provides important advice on the management of potential renal and bone effects of TDF in children and adolescent patients with chronic hepatitis B aged 2 to <18 years, and on the dosing recommendations for TDF in this population.[1–5]

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 (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
- ✓ TDF should not be used in children and 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. Also consider interrupting treatment with TDF in case of progressive decline of renal function when no other cause has been identified
- ✓ 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 and adolescents with renal impairment. TDF should not be initiated in children and adolescents with renal impairment and should be discontinued in children and adolescents who develop renal impairment during TDF therapy.

The recommendations for monitoring renal function in children and adolescent patients without renal risk factors prior to and during TDF therapy are provided in Table 1. 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 TDF	During 1st 3 months on TDF	>3 months on TDF
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 TDF treatment. Also consider interrupting treatment with TDF in case of progressive decline of renal function when no other cause has been identified.

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

Management of bone effects

TDF may cause a reduction in BMD.

Reductions in BMD have been reported in HBV infected children and adolescents. The BMD Z-scores observed at 48 weeks (children 2 to <12 years of age) or at 72 weeks (adolescents 12 to <18 years of age) in subjects who received TDF were lower than those observed in subjects who received placebo.

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 Viread in children and adolescents

Viread is approved for the treatment of chronic hepatitis B in children and adolescents 2 to <18 years of age with compensated liver disease and evidence of immune active disease, i.e. active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. The decision to treat children and adolescent patients should be based on careful consideration of individual patient needs and with reference to current paediatric treatment guidelines including the value of baseline histological information. The benefits of long-term virologic suppression with continued therapy must be weighed against the risk of prolonged treatment, including the emergence of resistant hepatitis B virus and the uncertainties as regards the long term impact of bone and renal toxicity. No data are currently available in children with chronic hepatitis B aged under 2 years.[1–5]

The following formulations of Viread are available for use in children and adolescents depending on age and weight:[1–5]

Table 2: Formulations available for children and adolescents[1–5]

Age (years)	Body Weight (kg)	Tenofovir disoproxil 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 per kilogram of body weight once daily taken with food. 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 HBV-infected children and adolescents aged 2 to <18 years are as follows:[2]

Table 3: Dosing of Viread 33 mg/g granules for children and adolescents[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

Reporting of suspected adverse reactions

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 via the national reporting system:

Sir Temi Żammit Buildings,
Malta Life Sciences Park,
San Ġwann SĠN 3000
Malta
www.medicinesauthority.gov.mt/adrportal

References

1. Summary of Product Characteristics for VIREAD 245 mg film-coated tablets.
2. Summary of Product Characteristics for VIREAD 33 mg/g granules.
3. Summary of Product Characteristics for VIREAD 123 mg film-coated tablets.
4. Summary of Product Characteristics for VIREAD 163 mg film-coated tablets.
5. Summary of Product Characteristics for VIREAD 204 mg film-coated tablets.

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