Renal Management and Dose Adjustment Advice for Healthcare Professionals with Adult Patients Receiving Tenofovir Disoproxil

HIV-positive patients are at increased risk of renal impairment, requiring baseline and subsequent renal monitoring. For those adult patients on tenofovir-based regimens specific recommendations are detailed below.

Important Points to Consider

- ✔ Check all patients' creatinine clearance before starting tenofovir therapy
- ✔ During tenofovir 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
- ✔ In patients with renal impairment, tenofovir should only be used if the potential benefits of treatment outweigh the potential risks, and the daily dose of tenofovir may need to be adjusted (see Table 2) or the dosing interval of tenofovir may need to be prolonged
- ✔ Consider interrupting treatment with tenofovir in patients with creatinine clearance decreased to <50 mL/min or decreases in serum phosphate to <1.0 mg/dL (0.32 mmol/L). 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 renal safety profile

In tenofovir clinical studies and post-marketing safety surveillance, rare events of renal failure, renal impairment, and proximal 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.

Monitoring of renal function

The recommendations for monitoring renal function in 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	Creatinine clearance and serum phosphate	Creatinine clearance and serum phosphate

If serum phosphate is <1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to <50 mL/min in any patient receiving tenofovir, renal function should be re-evaluated within 1 week, including measurements of blood glucose, blood potassium and urine glucose concentrations.

Consideration should also be given to interrupting treatment with tenofovir in patients with creatinine clearance decreased to <50 mL/min or decreases in serum phosphate to <1.0 mg/dL (0.32 mmol/L) or 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 must 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. A 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.

Use in Renal Impairment

In patients with renal impairment, tenofovir should only be used if the potential benefits of treatment outweigh the potential risks, and close monitoring of renal function is recommended. Tenofovir is principally eliminated via the kidney and exposure to tenofovir increases in patients with renal dysfunction. Limited data from clinical studies support once daily dosing of tenofovir in patients with mild renal impairment (creatinine clearance 50–80 mL/min).
For treatment of HIV-1 infection in adults for whom a solid dosage form is not appropriate other suitable formulations should be checked for their availability.

For treatment of HIV infection in adult patients for whom a solid dosage form is not appropriate or when reduced doses are needed that cannot be achieved using the 245 mg film-coated tablets formulation or fixed-dose combinations containing tenofovir disoproxil, other suitable formulations should be checked for their availability. If no alternative treatment is available, prolonged dosage intervals using tenofovir disoproxil 245 mg film-coated tablets may be used, as shown in Table 2. Limited clinical study data suggests that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response.

Table 2: Recommended daily dose adjustments for patients with renal impairment

	Creatinine clearance (mL/min)			Haemodialysis patients
	50–80	30–49*	10-29*	
tenofovir	Administration of 245 mg once daily (no adjustment with tenofovir disoproxil Mylan is possible)	Administration of 245 mg every 48 hours	Administration of 245 mg every 72-96 hours (dosing twice a week)*	245 mg tenofovir disoproxil may be administered every 7 days following completion of a haemodialysis session**
tenofovir/ emtricitabine	Administration of 245 mg once daily (no adjustment with tenofovir disoproxil Mylan is possible)	Administration of 245 mg every 48 hours	Not recommended for use in patients with severe renal impairment (creatinine clearance <30mL/ min)	Not recommended

* These dose adjustments have not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored.

** Assuming 3 haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis. No dosing recommendations can be given for non-haemodialysis patients receiving tenofovir with creatinine clearance <10 mL/min.

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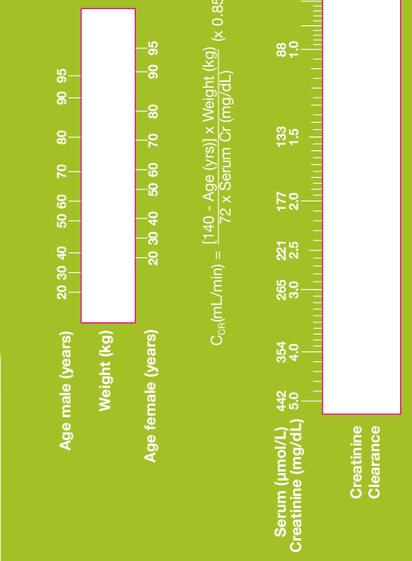
Creatinine clearance slide ruler



Instructions for use

1. Line up the weight of the patient with his/her age
2. Without shifting the scale, you can now read the serum creatinine and creatinine clearance

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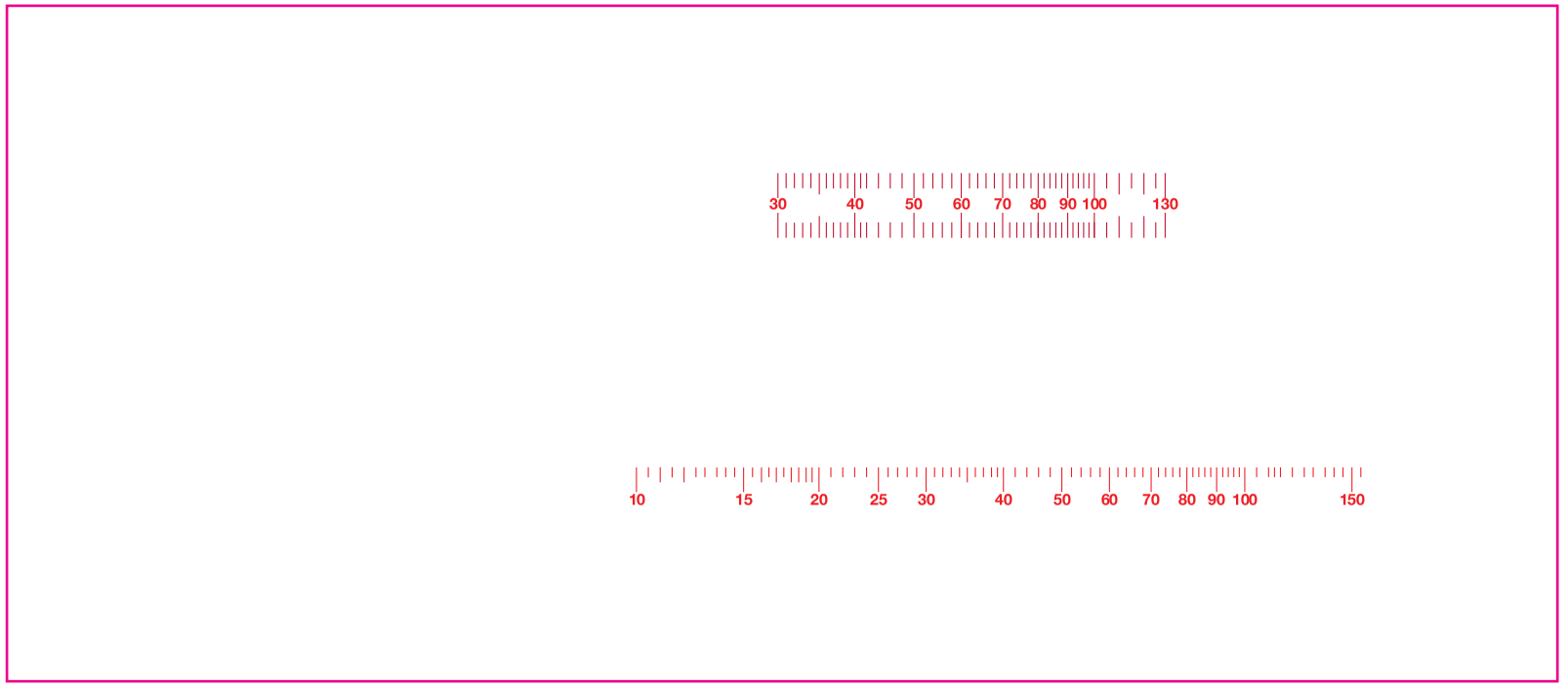
Reporting of side effects

Healthcare providers are asked to report any suspected adverse reactions. For any side effects please report to the Medicines Authority at http://www.medicinesauthority.gov.mt/adrportal or to the local representative of Mylan S.A.S. : V.J. Salomone Pharma Ltd., Upper Cross Road, Marsa MRS1542, Malta, Tel: +356 21 220 174 and 24h PV mobile +356 99644126.
By reporting side effects you can help provide more information on the safety of this medicine.

Mylan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