RENAL RISK MINIMISATION MATERIAL:
TENOFOVIR DISOPROXIL FOR *ADULTS* WITH CHRONIC HEPATITIS B

Important points to consider

- Check all patients' creatinine clearance before starting tenofovir disoproxil therapy
- During tenofovir disoproxil 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 disoproxil should only be used if the potential benefits of treatment outweigh the potential risks, and the daily dose of tenofovir disoproxil may need to be adjusted (see Table 2) or the dosing interval of tenofovir disoproxil may need to be prolonged (see Table 3)
- Consider interrupting treatment with tenofovir disoproxil 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 disoproxil 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 disoproxil renal safety profile in chronic hepatitis B (CHB) studies

In studies of patients with compensated CHB, ≤1.5% of patients who received tenofovir disoproxil throughout 288 weeks had a confirmed renal event (≥0.5 mg/dL increase in serum creatinine, serum phosphate <2 mg/dL, or creatinine clearance <50 mL/min).

Post-marketing safety surveillance (all indications)

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 disoproxil 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 disoproxil	During 1st 3 months on tenofovir disoproxil	>3 months on tenofovir disoproxil
Frequency	At baseline	At 2 to 4 weeks and 3 months	Every 3 to 6 months
Parameter	Creatinine clearence	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 disoproxil, 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 disoproxil 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 disoproxil 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. 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 disoproxil and with risk factors for renal dysfunction. If tenofovir disoproxil is co-administered with an NSAID, renal function should be monitored adequately.

Use in renal impairment

In adult patients with renal impairment, tenofovir disoproxil should only be used if the potential benefits of treatment outweigh the potential risks, and close monitoring of renal function is recommended. Tenofovir disoproxil is principally eliminated via the kidney and exposure to tenofovir disoproxil increases in patients with renal dysfunction. Limited data from clinical studies support once daily dosing of tenofovir disoproxil in patients with mild renal impairment (creatinine clearance 50–80 mL/min).

Administration of tenofovir disoproxil 33mg/g granules to provide a reduced daily dose of tenofovir disoproxil is recommended in adult patients with creatinine clearance <50 mL/min, including haemodialysis patients, as shown in Table 2. For patients unable to take tenofovir disoproxil granules, or if tenofovir disoproxil granules are not available, prolonged dosage intervals using tenofovir disoproxil 245 mg film-coated tablets may be used (Table 3).

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

	Creatinine clearance (mL/min)				Haemodialysis patients*
	50-80	30-49*	20-29*	10-19*	
Tenofovir disoproxil 33 mg/g granules	Administration of 245mg (7.5 scoops) of granules once daily (no adjustment required)	Administration of 132mg (4 scoops) of granules once daily.	Administration of 65mg (2 scoops) of granules once daily.	Administration of 33mg (1 scoop) of granules once daily.	16.5mg (0.5 scoop) of granules may be adminstered following completion of each 4 hour haemodialysis session.

*These dose adjustments have not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored. No dosing recommendations can be given for non-haemodialysis patients receiving tenofovir disoproxil 33 mg/g granules with creatinine clearance <10 mL/min.

The dosing interval adjustment guidelines for patients with creatinine clearance <50mL/min are shown in Table 3 below.

Table 3: Dosing interval adjustments for patients with renal impairment

	Creatinine clearance (mL/min)			Haemodialysis patients*
	50-80	30-49	10-29	
Tenofovir disoproxil	Administration of 245 mg once daily (no adjustment required)	For patients unable to take 33mg/g granules, administration of 245 mg every 48 hours*	For patients unable to take 33mg/g granules and with no alternative treatment available, prolonged dose intervals may be used: 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**

*This dose interval adjustment has not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in these patients. Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response.

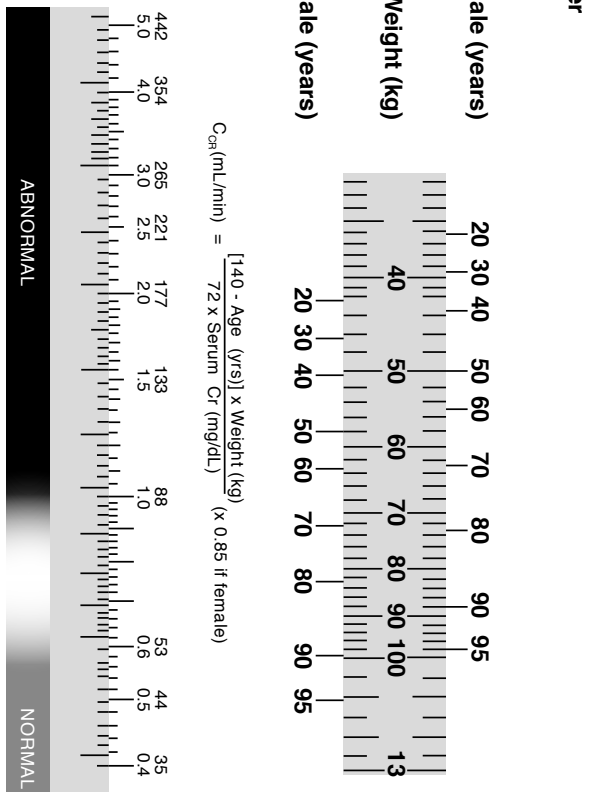
**Assuming 3 haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis. No dosing recommendations can be given for non-haemodialysis patients receiving tenofovir disoproxil 245 mg film-coated tablets with creatinine clearance <10 mL/min.

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

Please note that this is an estimation of creatinine clearance and may be inaccurate in certain situations eg: the elderly, extremes of BMI, rapidly changing kidney function.



$$C_{CR}(mL/min) = \frac{[140 - Age\ (yrs)] \times Weight\ (kg)}{72 \times Serum\ Cr\ (mg/dL)} \quad (\times 0.85 \text{ if female})$$