SHARED CARE ARRANGEMENT AND PRESCRIBING INFORMATION FOR TENOFOVIR DISOPROXIL

Note: This document should be read in conjunction with the current Summary of Product Characteristics (SmPC).

Patient safety is paramount. The prescriber who prescribes the medicine legally assumes clinical responsibility for the drug and the consequences of its use.

GENERIC AND BRAND NAME (formulations and strength)

Name: Tenofovir Disoproxil

Formulation: Film Coated Tablets and Granules

Strength: 245mg Film Coated Tablets and 33mg/g Granules

STATUS OF MEDICINE

Licence status: Licensed

Formulary status: Available for restricted use under specialist supervision.
Treatment may be initiated in Primary Care on the recommendation of a consultant/specialist.

Black triangle medicine: Yes ☐ No ☒

Risk Minimisation Materials (RMM): Yes ☒ No ☐

Tenofovir Disoproxil for Adolescent Children with Chronic Hepatitis B and Tenofovir Disoproxil for Adults with Chronic Hepatitis B (available from https://www.medicines.org.uk/emc/product/9150/rmms#about-medicine)

CONDITION(S) TO BE TREATED

Active chronic hepatitis B infection in patients ≥16 years with hepatitis B e-antigen (HBeAg) positive or negative infection, with at least 2 of the following 3 criteria, or as per the "indications for treatment" in the European Association for the Study of the Liver (EASL) Guidelines for Hepatitis B virus (HBV) infection.

- HBV DNA >2,000IU/mL
- ALT >Upper Limit of Normal (ULN)
- At least moderate liver necroinflammation or fibrosis either on liver biopsy or non-invasive test.

Active chronic hepatitis B infection in patients ≥18 years with HBeAg positive or negative infection with compensated or decompensated cirrhosis and any detectable HBV DNA level, regardless of alanine transaminase (ALT) levels.

Patients with HBV DNA >20,000IU/mL and ALT >2xULN regardless of degree of liver fibrosis.

<table>
<tr><th colspan="2">TYPICAL DOSAGE REGIME</th></tr>
<tr><td>Licensed dose</td><td>245mg (one tablet or 7.5 scoops of granules) once daily with food</td></tr>
<tr><td>Route of administration</td><td>Oral</td></tr>
<tr><td>Recommended starting dose</td><td>245mg (one tablet or 7.5 scoops of granules) once daily with food</td></tr>
<tr><td>Titration dose/increment</td><td>N/A</td></tr>
<tr><td>Maximum dose</td><td>245mg (one tablet or 7.5 scoops of granules) once daily with food</td></tr>
<tr><td>Situations requiring dose adjustment</td><td>Renal Impairment (calculated creatinine clearance <50mL/min) or renal replacement therapy.

An online creatinine clearance calculator can be found at https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation. Please use ideal body weight where fat or extremes of muscle mass are likely to be the major contributor to body mass. Where the patient's actual body weight is less than their ideal body weight, actual body weight should be used instead.

<table>
<tr><th>Creatinine Clearance (mL/min)</th><th></th></tr>
<tr><td>≥50</td><td>245mg daily</td></tr>
<tr><td>30-49</td><td>132mg (4 scoops) of granules once daily or, for patients unable to take granules, 245mg every 48 hours</td></tr>
<tr><td>20-29</td><td>65mg (2 scoops) of granules once daily or, for patients unable to take granules, 245mg twice weekly</td></tr>
<tr><td>10-19</td><td>33mg (1 scoop) of granules once daily or, for patients unable to take granules, 245mg twice weekly</td></tr>
<tr><td><10 and non-haemodialysis</td><td>Not recommended</td></tr>
<tr><td>Haemodialysis (give dose after haemodialysis)</td><td>245mg weekly (following completion of haemodialysis session)</td></tr>
</table>
There is limited data on the use of tenofovir disoproxil in patients with renal impairment and therefore it should only be used if potential benefits outweigh the risks.</td></tr>
<tr><td>Duration of treatment</td><td>Long-term or until hepatitis B surface antigen (HBsAg) loss.

Stopping after some years might be considered in selected cases.

Cessation of treatment will be advised by Specialist Service.</td></tr>
</table>

RESPONSIBILITY OF ACUTE CARE/SPECIALIST SERVICE

- Assess patient at outpatient clinic and undertake baseline investigations (body weight, urea and electrolytes (including phosphate), creatinine (and calculation of creatinine clearance), full blood count, liver function tests, and HBV DNA, HBsAG and HBeAG have been reported.
- Recommend initiation of treatment to GP.
- Counsel the patient on how to take the medication correctly, including provision of information on possible adverse reactions.
- Check urea and electrolytes (including phosphate), creatinine (and calculate creatinine clearance) after 2 to 4 weeks of treatment, after 3 months of treatment and then every 3 months thereafter for the first 12 months. These parameters will then be checked at least 6 monthly at clinic (but more frequently in patients at risk of renal impairment, e.g. continuation of 3 monthly monitoring in diabetic patients).
- Check liver function tests and AST every 3 months for the first 12 months of treatment then 6 monthly thereafter.
- Check body weight, full blood count and HBV DNA every 3 months for the first 12 months of treatment then 6 monthly thereafter.
- Patients on treatment will be seen at clinic after 2 to 4 weeks of treatment, after 3 months of treatment and then every 3 months thereafter for the first 12 months. They will then be seen at least 6 monthly thereafter (if no abnormalities).
- After each clinic visit a formal letter detailing clinical review, blood results and recommendations will be sent to the GP. If any immediate action is required, a clinical contact note will be completed in addition to a formal letter.
- Patients who discontinue treatment with tenofovir disoproxil will be reviewed at the specialist clinic. The frequency and duration of follow-up will be determined by the specialist service.

ADMINISTRATIVE RESPONSIBILITIES OF PRIMARY CARE

For the first 12 months of treatment, all blood monitoring will be undertaken at the outpatient clinic.

After the first 12 months of treatment, monitoring of urea and electrolytes (including phosphate), creatinine (and calculated creatinine clearance), liver function tests and AST should be undertaken every 3 months. As patients will be seen at the outpatient clinic every 6 months, this will require the practice to perform the afore-mentioned blood monitoring every 6 months (3 months after each clinic review).

In patients at risk of renal impairment, monthly monitoring of renal function may be required, however, this will be clarified by the specialist service on a case by case basis.

A Practice agreeing to prescribe tenofovir disoproxil should:

- Ensure that the relevant monitoring requirements are undertaken at the correct frequency.
- Ensure that the test results are checked for any abnormality as soon as the results are available.
- Ensure abnormal results are acted upon promptly.
- Only continue to prescribe medication if it is being satisfactorily monitored.
- Contact the consultant in the event of a drug reaction, monitoring abnormality (see over), or if you are concerned in any way regarding the current treatment regime.
- Be alert for any of the known adverse reactions.

CLINICIAL CARE WHICH IS THE RESPONSIBILITY OF THE PRESCRIBING CLINICIAN

1. Prescribe medication every 3 months under guidance of consultant, this is to link in with monitoring and review requirements.
2. Check before prescribing each instalment of medication that the monitoring is up to date and that results are within the normal range.
3. Conduct recommended laboratory tests and contact hospital consultant to advise if results are out with range (see below).
4. Ensure no interacting medications are prescribed in primary care. The University of Liverpool HEP Drug Interactions checker can be used to do this (available from: https://www.hep-druginteractions.org/checker).
5. Monitor for concordance with therapy.
6. Report any adverse events to consultant and the MHRA using the Yellow Card System.
7. When writing laboratory request forms always include details of the patient's medication.

Note: In addition to absolute values for haematological or biochemical indices a rapid change or a consistent upward/downward trend in any value should prompt caution and extra vigilance.

If something unexpected occurs contact consultant. Notify the consultant if the drug is stopped.

DISCUSS WITH THE CONSULTANT IF ANY OF THE FOLLOWING OCCURS

- **>2-fold rise in ALT or Alk Phos** (from baseline). Note elevated ALT is indication for initiating treatment
- **Creatinine Clearance <50mL/min**
  - renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations
- **Phosphate <0.48mmol/L**
  - renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations

Table 1: Monitoring requirements for patients on tenofovir disoproxil

		Time on tenofovir disoproxil treatment →					
	Prior to treatment (baseline)	**2 to 4 weeks**	**3 months**	**6 months**	**9 months**	**12 months**	**>12 months**
Urea and electrolytes (including phosphate and creatinine (and calculated creatinine clearance))	At clinic	At clinic	At clinic	At clinic	At clinic	At clinic	Check every 3 months. As the patient will be seen at clinic every 6 months, this will require the GP to check, U+Es (including phosphate), creatinine (Including creatinine clearance) and liver function tests twice per year (3 months after each clinic review).
Liver function tests	At clinic	Not required	At clinic	At clinic	At clinic	At clinic	
HBV DNA	At clinic	Not required	At clinic	At clinic	At clinic	At clinic	

RESPONSIBILITY OF OTHER HEALTHCARE PROFESSIONALS

N/A

RESPONSIBILITY OF THE PATIENT

Take medication regularly as directed by the specialist/doctor.

Attend hospital and GP clinic appointments as requested by specialist/GP practice. Failure to attend appointments may result in medication being reviewed/stopped.

Report any adverse effects/illness to the specialist/GP and present rapidly to specialist/GP should their condition significantly worsen

PRESCRIBING INFORMATION

For specific product information consult the current summary of product characteristics (http://emc.medicines.org.uk/), the BNF/BNF for Children (https://www.medicinescomplete.com/mc/index.htm)

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

PREGNANCY

Discuss with the hospital specialist.

The use of tenofovir disoproxil may be considered during pregnancy, if necessary. A large amount of data in now available on the use of tenofovir disoproxil in pregnant women which indicates no malformations or foetal/neonatal toxicity associated with its use.

In the literature, exposure to tenofovir disoproxil in the third trimester of pregnancy has been shown to reduce the risk of HBV transmission from mother to infant if tenofovir disoproxil is given to mothers, in addition to hepatitis B immune globulin and hepatitis B vaccine in infants.

BREAST-FEEDING

Discuss with the hospital specialist.

Generally, if the newborn is adequately managed for hepatitis B prevention at birth, a mother with hepatitis B may breastfeed her infant.

Tenofovir is excreted in human milk at very low levels and exposure of infants through breastmilk is considered negligible. Although there is limited long term data, no adverse reactions have been reported in breastfed infants, and HBV-infected mothers using tenofovir disoproxil may breastfeed.

COMMON SIDE EFFECTS AND THEIR MANAGEMENT

Side-effect	Management
Weakness (asthenia), rash, vomiting, diarrhoea, nausea (very common (occurring in ≥ 1/10 patients)). Headache, abdominal pain, abdominal distension, flatulence, fatigue (common (occurring in ≥1/100 to <1/10 patients))	These side-effects are usually mild and self-limiting and the patient should remain on treatment. If they become severe or the GP is concerned, please contact the hospital specialist.
Metabolic disturbance secondary to renal tubular toxicity: increased creatinine (uncommon (occurring in ≥1/1,000 to <1/100 patients)), hypophosphataemia (very common), hypokalaemia (uncommon).	Renal function (creatinine clearance and serum phosphate) is monitored prior to commencing treatment and during treatment (see above).If abnormal results occur then contact hospital specialist as per guidance above.
Increased transaminases (common)	Discuss with hospital specialist as per guidance above.
Osteomalacia (manifested as bone pain and infrequently contributing to fractures) (rare (occurring in ≥1/10,000 to <1/1,000 patients)	Discuss with hospital specialist.
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.	Discuss with hospital specialist.

For a full list of uncommon and rare side effects, please see SmPC.

COMMON DRUG INTERACTIONS (for a full list see SmPC and https://www.hep-druginteractions.org/)

Tenofovir Disoproxil should not be administered concomitantly with other medicinal products containing tenofovir disoproxil or tenofovir alafenamine.

Since tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir disoproxil with medicinal products that reduce renal function may increase serum concentrations of tenofovir and/or the co-administered medicinal products.

Given that tacrolimus can affect renal function, close monitoring is recommended when it is co-administered with tenofovir disoproxil.

If concomitant use of tenofovir disoproxil with nephrotoxic agents is unavoidable, renal function should be monitored at least 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 on a weekly basis initially. Patients should be counselled to avoid over the counter NSAIDs prior to starting treatment.

ADVERSE DRUG REPORTING

If an adverse reaction should occur inform relevant medical practitioner as soon as possible.

Report to the MHRA using the Yellow Card System https://yellowcard.mhra.gov.uk/

REFERENCES

1. European Association for the Study of the Liver (EASL). *EASL 2017 Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection*. Available from: https://easl.eu/wp-content/uploads/2018/10/HepB-English-report.pdf [Accessed 24th October 2023]
2. Specialist Pharmacy Service (SPS). *Safety in Lactation: Viral Hepatitis.* Available from https://www.sps.nhs.uk/articles/safety-in-lactation-viral-hepatitis/ [Accessed 24th October 2023]
3. Cipla EU Ltd, Summary of Product Characteristics. *Tenofovir Disoproxil 245mg film-coated tablets.*Available from https://www.medicines.org.uk/emc/product/9932/smpc# [Accessed 24th October 2023]
4. Martindale: The Complete Drug Reference. *Tenofovir.* Available from https://www.medicinescomplete.com/#/browse/martindale [Accessed 12th May 2024]

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION

In the event of a concern being raised, the primary care practitioner should contact the referring consultant via the hospital switchboard, via their secretary, by e-mail or letter, whichever is more appropriate. If the concern is urgent, and out of hours advice is required, the on call GI Registrar may be contacted via switchboard.

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