No dosing recommendations can be given for patients with CrCl < 15 mL/min who are not receiving haemodialysis (see section 4.4).

Hepatic impairment

No dose adjustment of Vemlidy is required in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Vemlidy in children younger than 12 years of age, or weighing < 35 kg, have not yet been established. No data are available.

Method of administration

Oral administration. Vemlidy film-coated tablets should be taken with food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

HBV transmission

Patients must be advised that Vemlidy does not prevent the risk of transmission of HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Patients with decompensated liver disease

There are no data on the safety and efficacy of Vemlidy in HBV-infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score ≥ 9 (i.e. class C). 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 (see section 5.2).

Exacerbation of hepatitis

Flares on treatment

Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum alanine aminotransferase (ALT). After initiating antiviral therapy, serum ALT may increase in some patients. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Flares after treatment discontinuation

Acute exacerbation of hepatitis has been reported in patients who have discontinued treatment for hepatitis B, usually in association with rising HBV DNA levels in plasma. The majority of cases are self-limited but severe exacerbations, including fatal outcomes, may occur after discontinuation of treatment for hepatitis B. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of treatment for hepatitis B. If appropriate, resumption of hepatitis B therapy may be warranted.

In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Renal impairment

Patients with creatinine clearance < 30 mL/min

The use of Vemlidy once daily in patients with CrCl ≥ 15 mL/min but < 30 mL/min and in patients with CrCl < 15 mL/min who are receiving haemodialysis is based on very limited pharmacokinetic data and on modelling and simulation. There are no safety data on the use of Vemlidy to treat HBV-infected patients with CrCl < 30 mL/min.

The use of Vemlidy is not recommended in patients with CrCl < 15 mL/min who are not receiving haemodialysis (see section 4.2).

Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

Patients co-infected with HBV and hepatitis C or D virus

There are no data on the safety and efficacy of Vemlidy in patients co-infected with hepatitis C or D virus. Co-administration guidance for the treatment of hepatitis C should be followed (see section 4.5).

Hepatitis B and HIV co-infection

HIV antibody testing should be offered to all HBV-infected patients whose HIV-1 infection status is unknown before initiating therapy with Vemlidy. In patients who are co-infected with HBV and HIV, Vemlidy should be co-administered

with other antiretroviral agents to ensure that the patient receives an appropriate regimen for treatment of HIV (see section 4.5).

Co-administration with other medicinal products

Vemlidy should not be co-administered with products containing tenofovir alafenamide, tenofovir disoproxil fumarate or adefovir dipivoxil.

Co-administration of Vemlidy with certain anticonvulsants (e.g. carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g. rifampicin, rifabutin and rifapentine) or St. John's wort, all of which are inducers of P-glycoprotein (P-gp) and may decrease tenofovir alafenamide plasma concentrations, is not recommended.

Co-administration of Vemlidy with strong inhibitors of P-gp (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Co-administration is not recommended.

Lactose intolerance

Vemlidy contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Vemlidy should not be co-administered with medicinal products containing tenofovir disoproxil fumarate, tenofovir alafenamide or adefovir dipivoxil.

Medicinal products that may affect tenofovir alafenamide

Tenofovir alafenamide is transported by P-gp and breast cancer resistance protein (BCRP). Medicinal products that are P-gp inducers (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital or St. John's wort) are expected to decrease plasma concentrations of tenofovir alafenamide, which may lead to loss of therapeutic effect of Vemlidy. Co-administration of such medicinal products with Vemlidy is not recommended.

Co-administration of Vemlidy with medicinal products that inhibit P-gp and BCRP may increase plasma concentration of tenofovir alafenamide. Co-administration of strong inhibitors of P-gp with Vemlidy is not recommended.

Tenofovir alafenamide is a substrate of OATP1B1 and OATP1B3 *in vitro*. The distribution of tenofovir alafenamide in the body may be affected by the activity of OATP1B1 and/or OATP1B3.

Effect of tenofovir alafenamide on other medicinal products

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor or inducer of CYP3A *in vivo*.

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 *in vitro*. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes.

Drug interaction information for Vemlidy with potential concomitant medicinal products is summarised in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔"; twice daily as "b.i.d.", single dose as "s.d.", once daily as "q.d."; and intravenously as "IV"). The drug interactions described are based on studies conducted with tenofovir alafenamide, or are potential drug interactions that may occur with Vemlidy.

Table 1: Interactions between Vemlidy and other medicinal products

Medicinal product by therapeutic areas	Effects on drug levels.[a,b] Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}	Recommendation concerning co-administration with Vemlidy
ANTICONVULSANTS		
Carbamazepine (300 mg orally, b.i.d.) Tenofovir alafenamide[c] (25 mg orally, s.d.)	*Tenofovir alafenamide* ↓ C_{max} 0.43 (0.36, 0.51) ↓ AUC 0.45 (0.40, 0.51) *Tenofovir* ↓ C_{max} 0.70 (0.65, 0.74) ↔ AUC 0.77 (0.74, 0.81)	Co-administration is not recommended.
Oxcarbazepine Phenobarbital	Interaction not studied. *Expected:*	Co-administration is not recommended.

	↓ Tenofovir alafenamide	
Phenytoin	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Midazolam[d] (2.5 mg orally, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Midazolam* ↔ C_{max} 1.02 (0.92, 1.13) ↔ AUC 1.13 (1.04, 1.23)	No dose adjustment of midazolam (administered orally or IV) is required.
Midazolam[d] (1 mg IV, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Midazolam* ↔ C_{max} 0.99 (0.89, 1.11) ↔ AUC 1.08 (1.04, 1.14)	
ANTIDEPRESSANTS		
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[c] (10 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 1.00 (0.86, 1.16) ↔ AUC 0.96 (0.89, 1.03) *Tenofovir* ↔ C_{max} 1.10 (1.00, 1.21) ↔ AUC 1.02 (1.00, 1.04) ↔ C_{min} 1.01 (0.99, 1.03)	No dose adjustment of Vemlidy or sertraline is required.
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[c] (10 mg orally, q.d.)	*Sertraline* ↔ C_{max} 1.14 (0.94, 1.38) ↔ AUC 0.93 (0.77, 1.13)	
ANTIFUNGALS		
Itraconazole Ketoconazole	Interaction not studied. *Expected:* ↑ Tenofovir alafenamide	Co-administration is not recommended.
ANTIMYCOBACTERIALS		
Rifampicin Rifapentine	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
Rifabutin	Interaction not studied. *Expected:* ↓ Tenofovir alafenamide	Co-administration is not recommended.
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied. *Expected:* ↔ Sofosbuvir ↔ GS-331007	No dose adjustment of Vemlidy or sofosbuvir is required.