1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VIREAD 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of tenofovir disoproxil fumarate, equivalent to 245 mg of tenofovir disoproxil.

Contains sugar: Lactose monohydrate 165,84 mg

For full list of excipients, see section 6.1.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE, OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (see SECTION 4.4).

THE SAFETY AND EFFICACY OF VIREAD HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV.

SEVERE ACUTE EXACERBATIONS OF HEPATITIS HAVE BEEN REPORTED IN HBV-INFECTED PATIENTS WHO HAVE DISCONTINUED ANTI-HEPATITIS B THERAPY, INCLUDING VIREAD. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ANTI-HEPATITIS B THERAPY, INCLUDING VIREAD. IF

APPROPRIATE, RESUMPTION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (see SECTION 4.4)

3. PHARMACEUTICAL FORM

Film-coated tablets

VIREAD film-coated tablets are almond-shaped, white, and debossed with “GILEAD” and “4331” on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VIREAD is indicated in adults and adolescents for:

HIV-1 infection

VIREAD is indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection in adults and in adolescent patients ≥ 12 years of age weighing ≥ 35 kg.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of VIREAD in treatment-naïve adults and in treatment-experienced adults.

Chronic Hepatitis B

VIREAD is indicated as monotherapy in HIV uninfected patients for the treatment of chronic

hepatitis B in adults and in adolescent patients ≥ 12 years of age weighing ≥ 35 kg with compensated liver disease, with evidence of active viral replication, persistent elevated ALT and histological evidence of active inflammation and/or fibrosis.

The following should be considered when initiating therapy with VIREAD for the treatment of HBV

infection:

- The indication in adults is based on safety and efficacy data from treatment of subjects who were nucleoside-treatment-naïve and subjects who were treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease.

4.2. Posology and method of administration

Posology

Adults

For the treatment of HIV-1 or chronic hepatitis B in adults: The dose of VIREAD (tenofovir disoproxil fumarate) is 300 mg once daily taken orally, without regard to food.

Adolescents 12 to 18 years of age

HIV-1 Infection and chronic hepatitis B (≥ 12 Years of Age and ≥ 35 kg).

Take one 300 mg VIREAD tablet (equivalent to tenofovir disoproxil 245 mg) once daily with or without food.

In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown.

Special populations

Renal impairment

Significantly increased medicine exposure occurred when VIREAD was administered to patients with moderate to severe renal impairment.

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of VIREAD, and periodically during VIREAD therapy.

Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in patients with mild renal impairment (see section 4.4).

Hepatic Impairment

Clinically relevant pharmacokinetic changes in patients with hepatic impairment are not observed. Therefore, no dose adjustment is required in patients with hepatic impairment.

Method of administration

For oral administration.

4.3. Contraindications

VIREAD is contraindicated in:

Patients with hypersensitivity to tenofovir or to any excipients in VIREAD (see section 6.1).

- Pregnancy and lactation (see section 4.6).
- VIREAD should not be used in combination with the fixed-dose combination medicines containing emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg, or other fixed dose combination medicines that contain tenofovir DF, since it is an ingredient of these medicines.

4.4. Special warnings and precautions for use

Patients to be treated with VIREAD for hepatitis B infection should be proven to be negative for HIV infection and should be tested regularly for HIV infection.

There are no study results demonstrating the effect of VIREAD on clinical progression of HIV-1.

General

VIREAD should not be co-administered with other medicines containing tenofovir disoproxil fumarate, or with medicines containing tenofovir alafenamide or adefovir dipivoxil.

Lactic Acidosis / Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues such as VIREAD alone, or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues such as VIREAD to any patient with known risk factors for

liver disease. However, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Lactic acidosis / hyperlactataemia

Use of VIREAD can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2 to 5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once hyperlactataemia has resolved, use medicines that are less likely to cause lactic acidosis. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism).
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients. Caution should be exercised when administering VIREAD to patients with known risk factors for liver disease. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of VIREAD is increased due to decreased clearance. The dose of VIREAD should therefore be adjusted (see

section 4.2).

VIREAD is principally eliminated by the kidney. Renal insufficiency, elevated creatinine, renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported in association with the use of VIREAD (see section 4.8).

Renal monitoring

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy, and as clinically appropriate, during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil.

Bone effects

There is limited clinical experience with VIREAD in paediatric patients. In clinical studies of HIV-1 infected patients and HBV infected patients 12 to <18 years of age, decreases in median BMD Z-scores were observed following treatment with VIREAD.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

In Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving VIREAD + lamivudine + efavirenz (-2,2 % ± 3,9) compared with patients receiving stavudine + lamivudine + efavirenz (-1,0 % ± 4,6). Changes in BMD at the hip were similar

between the two treatment groups (-2,8 % ± 3,5 in the VIREAD group vs. -2,4 % ± 4,5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24 to 48 weeks of the study and this reduction was sustained through week 144. Twenty-eight percent of VIREAD-treated patients vs. 21 % of the stavudine-treated patients lost at least 5 % of BMD at the spine or 7 % of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in four patients in the VIREAD group and six patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group.

Except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir.
These manifest as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of VIREAD (see section 4.8). Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphataemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving medicines containing tenofovir DF (see section 4.4).

Bone monitoring should be considered for HIV and hepatitis B infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be

beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Patients with HIV and Hepatitis B or C virus co-infection

Due to the risk of development of HIV resistance, VIREAD should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV co-infected patients.

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Only relevant to lamivudine, tenofovir and emtricitabine (FTC): Discontinuation of VIREAD therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis and other generalised and/or focal mycobacterial infections, cytomegalovirus retinitis, cryptococcal meningitis, and *Pneumocystis jiroveci pneumonia*. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a

variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or post-natally to nucleoside analogues.
Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving VIREAD. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of VIREAD until diagnosis of pancreatitis is excluded.

Liver disease

Use of VIREAD can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of VIREAD has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Opportunistic infections

Patients receiving VIREAD should be advised that they may continue to develop opportunistic

infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

Excipients

VIREAD contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take VIREAD.

4.5. Interaction with other medicines and other forms of interaction

At concentrations substantially higher (~300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* medicine metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9 or CYP2E1. However, a small (6 %) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir is low.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of VIREAD with medicines that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered medicine, due to competition for this elimination pathway. Medicines that decrease renal function may also increase serum concentrations of tenofovir.

VIREAD has been evaluated in healthy volunteers in combination with abacavir, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir,

ledipasvir/sofosbuvir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, sofosbuvir, sofosbuvir/velpatasvir, tacrolimus, tipranavir/ritonavir.

No clinically significant interactions have been observed between VIREAD and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin or sofosbuvir.

Tables 2 and 3 summarise pharmacokinetic effects of co-administered medicine on VIREAD pharmacokinetics and effects of VIREAD on the pharmacokinetics of co-administered medicines.

Table 4 summarises the interaction between VIREAD and didanosine. When administered with multiple doses of VIREAD, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with VIREAD, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 2

Medicine Interactions: Changes in Pharmacokinetic Parameters for VIREAD in the Presence of the Co-administered Medicine

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**N**	**% Change of VIREAD Pharmacokinetic Parameters (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once daily	8	⇔	⇔	NC
Atazanavir	400 once daily x 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once daily	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔

Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Ledipasvir/ Sofosbuvir	90/400 once daily × 10 days	24	↑ 47 (↑ 37 to ↑ 58)	↑ 35 (↑ 29 to ↑ 42)	↑ 47 (↑ 38 to ↑ 57)
Ledipasvir/ Sofosbuvir		23	↑ 64 (↑ 54 to ↑ 74)	↑ 50 (↑ 42 to ↑ 59)	↑ 59 (↑ 49 to ↑ 70)
Ledipasvir/ Sofosbuvir	90/400 once daily x 14 days	15	↑ 79 (↑ 56 to ↑ 104)	↑ 98 (↑ 77 to ↑ 123)	↑ 163 (↑ 132 to↑197)
Ledipasvir/ Sofosbuvir	90/400 once daily x 10 days	14	↑ 32 (↑ 25 to ↑ 39)	↑ 40 (↑ 31 to ↑ 50)	↑ 91 (↑ 74 to ↑ 110)
Ledipasvir/ Sofosbuvir	90/400 once daily x 10 days	29	↑ 61		
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1 250 twice daily × 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1 000/100 twice daily x 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Sofosbuvir	400 single dose	16	↑ 25 (↑ 8 to ↑ 45)	⇔	⇔
Sofosbuvir/ Velpatasvir	400/100 once daily	24	↑ 55 (↑ 43 to ↑ 68)	↑ 30 (↑ 24 to ↑ 36)	↑ 39 (↑ 31 to ↑ 48)
Sofosbuvir/ Velpatasvir	400/100 once daily	29	↑ 55 (↑ 45 to ↑ 66)	↑ 39 (↑ 33 to ↑ 44)	↑ 52 (↑ 45 to ↑ 59)

Sofosbuvir/ Velpatasvir	400/100 once daily	15	↑ 77 (↑ 53 to ↑ 104)	↑ 81 (↑ 68 to ↑ 94)	↑ 121 (↑ 100 to ↑ 143)
Sofosbuvir/ Velpatasvir	400/100 once daily	24	↑ 36 (↑ 25 to ↑ 47)	↑ 35 (↑ 29 to ↑ 42)	↑ 45 (↑ 39 to ↑ 51)
Sofosbuvir/ Velpatasvir	400/100 once daily	24	↑ 44 (↑ 33 to ↑ 55)	↑ 40 (↑ 34 to ↑ 46)	↑ 84 (↑ 76 to ↑ 92)
Sofosbuvir/ Velpatasvir	400/100 once daily	30	↑ 46 (↑ 39 to ↑ 54)	↑ 40 (↑ 34 to ↑ 45)	↑ 70 (↑ 61 to ↑ 79)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔
Tipranavir/ Ritonavir[k]	500/100 twice daily	22	↓ 23 (↓ 32 to ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 twice daily (23 doses)	20	↓ 38 (↓ 46 to ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant medicine interactions between these medicines and VIREAD.

Table 3

Medicine Interactions: Changes in Pharmacokinetic Parameters for Co-administered Medicine in the Presence of VIREAD

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**N**	**% Change of Co-administered Medicine Pharmacokinetic Parameters (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once daily	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA

Atazanavir	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25 (↓ 42 to ↓ 3)	↓ 23 (↓ 46 to ↑ 10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Entecavir	1 mg once daily x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Methadone	40 to 110 once daily x 14 days	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1 250 twice daily x 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) once daily x 7 days	20	⇔	⇔	⇔
Ribavirin	600 once daily	22	⇔	⇔	NA
Saquinavir Ritonavir	Saquinavir/ Ritonavir 1 000/100 twice daily x 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29 (↑ 12 to ↑ 48) ⇔	↑ 47 (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔

Tipranavir	Tipranavir/Ritonavir 500/100 twice daily	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/Ritonavir 750/200 twice daily (23 doses)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

Table 4

Medicine Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of VIREAD

Didanosine Dose (mg)/ Method of Administration	**VIREAD Method of Administration**	**N**	**% Difference (90 % CI) vs. Didanosine 400 mg alone, Fasted**	
			C_{max}	**AUC**
Buffered tablets				
400 once daily x 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 ↑ 31 to ↑ 59)
Enteric-coated capsules				
400 once daily, fasted	With food, 2 hr after didanosine	26	↑ 48 (↑ 25 to↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once daily, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once daily, fasted	With food, 2 hr after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once daily, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once daily, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

Medicine interactions

When administered with VIREAD, the C_{max} and AUC of didanosine, administered as either the buffered or enteric-coated formulation, increased significantly (see Table 4). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-

associated adverse events, including pancreatitis, lactic acidosis[14] and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily. In adults weighing > 60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg.

When co-administered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (< 400 kcal, 20 % fat). Co-administration of didanosine buffered tablet formulation with VIREAD should be under fasted conditions. **Co-administration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.**

Since VIREAD is primarily eliminated by the kidneys, co-administration of VIREAD with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of VIREAD and/or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir.

Higher VIREAD concentrations could potentiate VIREAD-associated adverse events, including renal disorders.

Atazanavir and lopinavir/ritonavir have been shown to increase VIREAD concentrations. The mechanism of this interaction is unknown. **Patients receiving atazanavir and lopinavir/ritonavir and VIREAD should be monitored for VIREAD-associated adverse events. VIREAD should be discontinued in patients who develop VIREAD-associated**

adverse events.

VIREAD decreases the AUC and C_{min} of atazanavir. When co-administered with VIREAD, it is recommended that atazanavir 300 mg be given with ritonavir 100 mg. Atazanavir without ritonavir should not be co-administered with VIREAD.

Co-administration of tenofovir disoproxil fumarate and ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase tenofovir exposure. Patients receiving a regimen containing tenofovir disoproxil fumurate concomitantly with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.

In the treatment of chronic hepatitis B, VIREAD should not be administered in combination with adefovir dipivoxil.

VIREAD should be avoided with concurrent or recent use of a nephrotoxic medicines (e.g. high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)). Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on VIREAD. Some patients required hospitalisation and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

4.6. Fertility, pregnancy and lactation

VIREAD is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

VIREAD should not be taken during pregnancy (see section 4.3).

Breastfeeding

Nursing Mothers: HIV-infected mothers should not breastfeed their infants, to avoid risking postnatal transmission of HIV. Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk at low levels estimated neonatal concentrations 128 to 266 times lower than the tenofovir IC_{50}. VIREAD-associated risks, including the risk of developing viral resistance to tenofovir, in infants breastfed by mothers being treated with VIREAD are unknown.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving VIREAD** (see section 4.3).

4.7. Effects on ability to drive and use machines

VIREAD has minor influence on the ability to drive and operate machinery.

Since adverse reactions such as dizziness have been reported in patients receiving VIREAD, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that VIREAD does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Immune system disorders			Allergic reaction (including angioedema)

Metabolism and nutrition disorders			Hypophosphataemia, lactic acidosis, hypokalemia
Nervous system disorders	Dizziness, insomnia		
Respiratory, thoracic and mediastinal disorders			Dyspnoea
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, flatulence		Abdominal pain, increased amylase, pancreatitis
Hepato-biliary disorders			Increased liver enzymes (ALT, AST, gamma GT), hepatitis
Skin and subcutaneous tissue disorders			Rash, pruritus
Musculoskeletal and connective tissue disorders			Myopathy, osteomalacia (both associated with proximal renal tubulopathy), rhabdomyolysis, muscular weakness
Renal and urinary disorders			Renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, polyuria, intestinal nephritis (including acute cases)
General disorders and administrative site conditions			Asthenia, pyrexia

b) Paediatric population

Safety and effectiveness of VIREAD in paediatric patients younger than 12 years of age or less than 35 kg with chronic hepatitis B have not been established.

Use in adolescents

Adolescents 12 Years of Age and Older with HIV-1 infection.

The safety of VIREAD in adolescent patients aged 12 to less than 18 years is supported by data from one randomized trial in which VIREAD was administered to HIV1 infected treatment-

experienced subjects. In this trial, the pharmacokinetic profile of VIREAD was similar to that found to be safe and effective in adult clinical trials. In Study 321, 87 treatment-experienced subjects 12 to less than 18 years of age were treated with VIREAD (N=45) or placebo (N=42) in combination with an optimized background regimen (OBR) for 48 weeks. The mean baseline CD4 cell count was 374 cells/mm^3 and the mean baseline plasma HIV-1 RNA was 4.6 log_{10} copies/ml. At baseline, 90% of subjects harboured NRTI resistance-associated substitutions in their HIV-1 isolates. Overall, the trial failed to show a difference in virologic response between the VIREAD and placebo treatment groups. Subgroup analyses suggest the lack of difference in virologic response may be attributable to imbalances between treatment arms in baseline viral susceptibility to VIREAD and OBR.

Although changes in HIV-1 RNA in these highly treatment-experienced subjects were less than anticipated, the comparability of the pharmacokinetic and safety data to that observed in adults supports the use of VIREAD in adolescent 12 years of age and older who weigh greater than or equal to 35 kg and whose HIV-1 isolate is expected to be sensitive to VIREAD.[17] See sections 4.4 and 4.8. Safety and effectiveness of VIREAD in patients younger than 12 years of age with HIV-1 infection have not been established.

Adolescent Patients 12 Years of Age and Older with Chronic Hepatitis B

In Study 115, 106 HBeAg negative (9 %) and positive (91 %) subjects aged 12 to less than 18 years with chronic HBV infection were randomized to receive blinded treatment with VIREAD 300 mg (N =52) or placebo (N =54) for 72 weeks. At study entry, the mean HBV DNA was 8.1 log_{10} copies/ml and mean ALT was 101 U/L. Of 52 subjects treated with VIREAD, 20 subjects were nucleoside-naive and 32 subjects were nucleoside experienced. Thirty one of the 32 nucleoside-experienced subjects had prior lamivudine experience. At Week 72, 88 % (46/52) of subjects in the VIREAD group and 0 % (0/54) of subjects in the placebo group had HBV DNA <400 copies/ml. Among subjects with abnormal ALT at baseline, 74 % (26/35) of subjects receiving VIREAD had normalized ALT at Week 72 compared to 31 % (13/42) in the placebo group. One

VIREAD-treated subject experienced sustained HBsAg-loss and seroconversion to anti-HBs during the first 72 weeks of study participation.

Safety and effectiveness of VIREAD in patients younger than 12 years of age or less than 35 kg with chronic hepatitis B have not been established.

c) Other special populations

Use in the elderly

Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be done with caution, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy.

Patients with impaired renal function (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In Study 901, 600 mg VIREAD was administered to 8 patients orally for 28 days. The effects of higher doses are not known.

Treatment

If overdosage occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

VIREAD is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of VIREAD, a four-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 20.2.8 Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents

Pharmacotherapeutic group: Nucleoside and nucleotide reverse transcriptase inhibitors

ATC code: J05AF07

Mechanism of action

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate.

Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

Activity against HIV

Medicine resistance:

HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2 to 4-fold reduction in susceptibility to tenofovir. In addition, a K70E substitution in HIV-1 reverse transcriptase resulted in low-level reduced susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral medicines. In treatment-naïve patients treated with tenofovir DF + lamivudine + efavirenz, viral isolates from 8/47 (17 %) patients with virologic failure showed reduced susceptibility to tenofovir.

In treatment-experienced patients, 14/304 (4,6 %) of the tenofovir DF-treated patients with virologic failure through week 96 showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognised. The K65R mutation selected by tenofovir is also selected in some HIV-1-infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among

these medicines may occur in patients whose virus harbours the K65R mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3, zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) showed a 3,1-fold decrease in the susceptibility to tenofovir. Multinucleoside-resistant HIV-1 with a T69S double-insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Activity against HBV

Cross-Resistance

Cross-resistance has been observed between HBV nucleoside/nucleotide analogue reverse transcriptase inhibitors including tenofovir.

In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V substitutions associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0,7- to 3,4-fold that of wild type virus. The rtL180M and rtM204I/V double substitutions conferred 3,4-fold reduced susceptibility to tenofovir.

HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V, and rtM250V substitutions associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0,6- to 6,9-fold that of wild type virus.

HBV strains expressing the adefovir resistance-associated substitutions rtA181V and/or rtN236T showed reductions in susceptibility to tenofovir ranging from 2,9- to 10-fold that of wild type virus. Strains containing the rtA181T substitution showed changes in susceptibility to tenofovir ranging from 0,9- to 1,5-fold that of wild type virus.

5.2. Pharmacokinetic properties

Absorption

Tenofovir disoproxil fumarate is a water-soluble diester pro-drug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25 %. Following oral administration of a single dose of tenofovir DF 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1,0 ± 0,4 hrs. C_{max} and AUC values are 296 ± 90 ng/ml and 2 287 ± 685 ng·h/mL, respectively.

The pharmacokinetics of tenofovir DF are dose proportional over a dose range of 75 mg to 600 mg and are not affected by repeated dosing.

Effects of food on oral absorption

Administration of tenofovir disoproxil fumarate following a high-fat meal (~700 to 1 000 kcal containing 40 to 50 % fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40 % and an increase in C_{max} of approximately 14 %. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ± 119 ng/ml and 3 324 ± 1 370 ng·h/mL following multiple doses of tenofovir disoproxil fumarate 300 mg once daily in the fed state, when meal content was not controlled.

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0,7 % and 7,2 % respectively, over the tenofovir concentration range 0,01 to 25 μg/ml. The volume of distribution at steady-state is 1,3 ± 0,6 L/kg and 1,2 ± 0,4 L/kg, following intravenous administration of tenofovir 1,0 mg/kg and 3,0 mg/kg.

Biotransformation

In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following IV administration of tenofovir, approximately 70 to 80 % of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single-dose oral administration of tenofovir disoproxil fumarate, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate 300 mg once daily (under fed conditions), 32 ± 10 % of the administered dose is recovered in urine over 24 hours.

Elimination

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Adolescents

Steady-state pharmacokinetics of tenofovir was evaluated in 8 HIV-1 infected adolescents (12 to less than 18 years). Mean (±SD) C_{max} and AUC_{tau} are 0,38 ± 0,13 µg and 3,39 ± 1,22 µg.hr/ml respectively. Tenofovir exposure achieved in these adolescents receiving oral daily doses of VIREAD 300 mg was similar to exposures achieved in adults receiving once-daily doses of VIREAD 300 mg.

Tenofovir exposure in HBV infected adolescents (12 to < 18 years of age) receiving oral daily dose of VIREAD 300 mg tablet was similar to exposures achieved in adults receiving once-daily doses of 300 mg.

Pharmacokinetic trials have not been performed in adolescents less than 12 years of age.

Elderly Patients

Pharmacokinetic trials have not been performed in the elderly (65 years and older).

Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg single dose have been studied in non-HIV-infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

Renal Impairment

The pharmacokinetics of tenofovir are altered in patients with renal impairment (see section 4.4). In patients with creatinine clearance < 50 ml/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} and $AUC_{0-\infty}$ of tenofovir were significantly increased (Table 1). It is recommended that tenofovir not be used in patients with creatinine clearance < 50 ml/min or in patients with ESRD who require dialysis.

Table 1

Pharmacokinetic Parameters (Mean ± SD) of Tenofovir[1] in Patients with Varying Degrees of Renal Function

Baseline Creatinine Clearance (ml/min)	**> 80 (N=3)**	**50 to 80 (N=10)**	**30 to 49 (N=8)**	**12 to 29 (N=11)**
C_{max} (ng/ml)	335,4 ± 31,8	330,4 ± 61,0	372,1 ± 156,1	601,6 ± 185,3
AUC $_{0-\infty}$ (ng.hr/mL)	2 184,5 ± 257,4	3 063,8 ± 927,0	6 008,5 ± 2 504,7	15 984,7 ± 7 223,0
CL/F (ml/min)	1 043,7 ± 115,4	807,7 ± 279,2	444,4 ± 209,8	177,0 ± 97,1
CL_{renal} (mL/min)	243,5 ± 33,3	168,6 ± 27,5	100,6 ± 27,5	43,0 ± 31,2

[1]300 mg, single dose of tenofovir DF

Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir DF, a four-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, titanium dioxide, triacetin.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

48 months shelf-life has been approved for product packed in high density polyethylene bottle.

36 months shelf life has been approved for product packed in aluminium blister packs.

6.4. Special precautions for storage

Store at or below 30 °C.

Do not use if seal over bottle opening is broken or missing or if there is evidence of tampering with the blister pack.

Keep the bottle tightly closed.

Keep in original packaging until required for use.

6.5. Nature and contents of container

VIREAD film-coated tablets are supplied as follows:

30 film-coated tablets are packed into high density polyethylene bottle with a white polypropylene child-resistant cap, together with a desiccant (1 gram silica gel high density polyethylene canister or sachet) and polyester fibre coil. The high density polyethylene bottles are sealed with an aluminium induction seal. The bottle is placed in an outer cardboard carton together with a leaflet.

30 film-coated tablets are packed in an aluminium blister strip with a polyvinylchloride inner lining sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

A40/20.2.8/0681

9. DATE OF FIRST AUTHORISATION

Date on registration certificate: 13 April 2007

10. DATE OF REVISION OF TEXT

Clinical approval: 24 November 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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