1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

VIREAD (film-coated tablet)

COMPOSITION

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

Excipients:

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

Contains sugar: Lactose monohydrate 165,84 mg

WARNINGS

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 WARNINGS AND SPECIAL PRECAUTIONS).

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 WARNINGS AND SPECIAL PRECAUTIONS)

CATEGORY AND CLASS

A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral agents. 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.

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.

Metabolism

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.

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

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.

The pharmacokinetics of tenofovir are altered in patients with renal impairment (see WARNINGS AND SPECIAL PRECAUTIONS). 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 (see CONTRAINDICATIONS).

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

INDICATIONS

HIV-1 infection

VIREAD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

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 18 years of age and older 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.

CONTRAINDICATIONS

VIREAD is contraindicated in:

- Patients with hypersensitivity to tenofovir or to any of the excipients in VIREAD (see COMPOSITION).
- Pregnancy and lactation (see HUMAN REPRODUCTION).

VIREAD should not be used in combination with the fixed-dose combination products containing emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg, or other fixed dose combination products that contain tenofovir DF, since it is an ingredient of these products.

WARNINGS AND SPECIAL PRECAUTIONS

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

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

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 agents that are less likely to cause lactic acidosis.
- Lactate 5 to10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, 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 DOSAGE AND DIRECTION FOR USE).

VIREAD is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of VIREAD (see CONTRAINDICATIONS and SIDE EFFECTS). 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 (see CONTRAINDICATIONS).

Bone effects

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.

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 SIDE EFFECTS). Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia 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 products containing tenofovir DF (see WARNINGS AND SPECIAL PRECAUTIONS).

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

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, cytomegalovirus retinitis, and cryptococcal meningitis. 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.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including VIREAD, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Effects on ability to drive and use machines

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 SIDE EFFECTS).

Excipients

Lactose warning:

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 e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take VIREAD.

INTERACTIONS

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 with other medicinal products 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, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin and saquinavir/ritonavir. 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 medicine 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[1] in the Presence of the Co-administered Medicine

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**N**	**% Change of VIREAD Pharmacokinetic Parameters[2] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once daily	8	⇔	⇔	NC
Adefovir	10 once daily	22	⇔	⇔	NC

dipivoxil					
Atazanavir[3]	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	⇔	⇔	⇔
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)

1. Patients received VIREAD 300 mg once daily

2. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated

3. Atazanavir prescribing information

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 agents 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[1] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once daily	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Adefovir dipivoxil	10 once daily	22	⇔	⇔	NA
Atazanavir[2]	400 once daily x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[2]	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[3] (↓ 42 to ↓ 3)	↓ 23[3] (↓ 46 to ↑ 10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
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[4]	40 to 110 once daily x 14 days[5]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1 250 twice daily x 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives[6]	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[7] (↑ 12 to ↑ 48) ⇔	↑ 47[7] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)

1. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable
2. Atazanavir Prescribing Information.
3. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2,3- and 4-fold higher than the

respective values observed for atazanavir 400 mg when given alone.

4. R-(active), S- and total methadone exposures were equivalent when dosed alone or with VIREAD. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
6. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD.
7. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are co-administered.

Table 4

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

Didanosine[1] Dose (mg)/Method of Administration[2]	**VIREAD Method of Administration[2]**	**N**	**% Difference (90 % CI) vs. Didanosine 400 mg alone, Fasted[3]**	
			C_{max}	**AUC**
Buffered tablets				
400 once daily[4] 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)

1. See WARNINGS AND SPECIAL PRECAUTIONS regarding use of didanosine with VIREAD.
2. Administration with food was with a light meal (~373 kcal, 20 % fat).
3. Increase = ↑; Decrease = ↓; No Difference = ⇔.
4. Includes 4 subjects weighing < 60 kg receiving ddI 250 mg.

Medicine interactions

When administered with VIREAD, 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 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.

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 agent (e.g. high-dose or multiple non-steroidal anti-inflammatory medicines (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.

HUMAN REPRODUCTION

The safety of VIREAD in pregnancy and lactation has not been established (see CONTRAINDICATIONS).

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response,VIREAD should not be used during pregnancy (see CONTRAINDICATIONS).

Lactation

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. The impact of this exposure in breastfed infants is 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 CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

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.

Chronic Hepatitis B

Safety and efficacy of VIREAD in patients younger than 18 years of age have not been established.

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

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 WARNINGS AND SPECIAL PRECAUTIONS).

SIDE EFFECTS

Immune system disorders

Frequency unknown: Allergic reaction (including angioedema)

Metabolism and nutrition disorders

Frequency unknown: Hypophosphataemia, lactic acidosis, hypokalemia

Nervous system disorders

Frequent: Dizziness, insomnia

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Dyspnoea

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, vomiting, flatulence

Frequency unknown: Abdominal pain, increased amylase, pancreatitis

Hepato-biliary disorders

Frequency unknown: Increased liver enzymes (ALT, AST, gamma GT), hepatitis

Skin and subcutaneous tissue disorders

Frequency unknown: Rash, pruritus

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: Myopathy, osteomalacia (both associated with proximal renal tubulopathy), rhabdomyolysis, muscular weakness

Renal and urinary disorders

Frequency unknown: 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

Frequency unknown: Asthenia, pyrexia

Safety and effectiveness of VIREAD in paediatric patients younger than 18 years of age or less

than 35 kg with chronic hepatitis B have not been established.

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.

Bone effects

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.

Patients with impaired renal function (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

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.

IDENTIFICATION

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

PRESENTATION

30 film-coated tablets are packed into a 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 a 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 are necessarily marketed.

STORAGE INSTRUCTIONS

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.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

A40/20.2.8/0681

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

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