PROFESSIONAL INFORMATION - CLEAN

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VIRONETO film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: lactose monohydrate 153,33 mg per tablet.

For full list of excipients, see section 6.1

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 section 4.4).

THE SAFETY AND EFFICACY OF VIRONETO HAS 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 VIRONETO. 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 VIRONETO. IF APPROPRIATE, RESUMPTION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (see section 4.4).

3 PHARMACEUTICAL FORM

Film-coated tablets.

White circular film-coated convex tablets, engraved TDF on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

HIV-1 infection

VIRONETO is indicated in combination with other antiretroviral medicines 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 VIRONETO in treatment-naïve adults and in treatment-experienced adults.

Chronic Hepatitis B

VIRONETO 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 VIRONETO 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 VIRONETO (tenofovir disoproxil fumarate) is 300 mg once daily taken orally, without regard to food.

Chronic Hepatitis B

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

Significantly increased medicine exposure occurred when VIRONETO was administered to patients with moderate to severe renal impairment (see section 4.3).

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with VIRONETO. 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 VIRONETO, and periodically during VIRONETO 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).

Method of administration

Oral use.

VIRONETO may be taken with or without food.

4.3 Contraindications

VIRONETO is contraindicated in:

- Patients with known hypersensitivity to tenofovir disoproxil fumarate or to any of the excipients of VIRONETO (see section 6.1).
- Pregnancy and lactation (see section 4.6).

VIRONETO 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 VIRONETO 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 VIRONETO on clinical progression of HIV-1.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, has been reported with the use of nucleoside analogues such as VIRONETO 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 VIRONETO 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 VIRONETO 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 VIRONETO 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 - 5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5 - 10 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 VIRONETO to patients with known risk factors for liver disease. Treatment with VIRONETO 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 VIRONETO is increased due to decreased clearance. The dose of VIRONETO should therefore be adjusted (see section 4.2).

VIRONETO 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 VIRONETO (see sections 4.3 and 4.8). It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy, and as clinically appropriate, during therapy with VIRONETO. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment (see section 4.3).

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 VIRONETO (see section 4.8). 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 medicines containing tenofovir DF (see section 4.4).

Bone monitoring should be considered for HIV 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), including components of VIRONETO. 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 professional information for these medicines. Patients co-infected with HIV and HBV who discontinue VIRONETO 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 VIRONETO 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 and 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 postnatally 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 signs or symptoms.

Pancreatitis

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

Liver disease

Use of VIRONETO can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of VIRONETO 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, interruption or discontinuation of treatment must be considered.

Opportunistic infections

Patients receiving VIRONETO may continue to develop opportunistic infections

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

The risk of HIV transmission to others

Patients must be advised that treatment with Vironeto, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Excipients

VIRONETO contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take VIRONETO.

Use in the elderly

Clinical studies 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.

Paediatric population

Safety and effectiveness in paediatric patients and patients < 18 years of age (or less than 35 kg) have not been established.

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 with other medicines is low.

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

VIRONETO 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 1 and 2 summarise pharmacokinetic effects of co-administered medicine on VIRONETO pharmacokinetics and effects of VIRONETO on the pharmacokinetics of co-administered medicines.

Table 3 summarises the medicine interaction between VIRONETO and didanosine. When administered with multiple doses of VIRONETO, 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 tenofovir, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 1

Medicine interactions: Changes in pharmacokinetic parameters for tenofovir[1] in the presence of the co-administered medicine

Co-administered medicine	**Dose of Co-administered medicine (mg)**	**N**	**% Change of Tenofovir Pharmacokinetic Parameters[2] (90 % CI)**		
			Cmax	**AUC**	**Cmin**
Abacavir	300 once daily	8	⇔	⇔	NC
Adefovir dipivoxil	10 once daily	22	⇔	⇔	NC
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 Tenofovir 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 medicines and tenofovir.

Table 2

Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of tenofovir

Co-administered medicine	**Dose of Co-administered medicine (mg)**	**N**	**% Change of Co-administered medicine Pharmacokinetic Parameters[1] (90 % CI)**		
			Cmax	**AUC**	**Cmin**
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)

Co-administered medicine	**Dose of Co-administered medicine (mg)**	**N**	**% Change of Co-administered medicine Pharmacokinetic Parameters[1] (90 % CI)**		
			Cmax	**AUC**	**Cmin**
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

Co-administered medicine	**Dose of Co-administered medicine (mg)**	**N**	**% Change of Co-administered medicine Pharmacokinetic Parameters[1] (90 % CI)**		
			Cmax	**AUC**	**Cmin**
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 Tenofovir. 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 Tenofovir.
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 3

Medicine interactions: Pharmacokinetic parameters for didanosine in the presence of tenofovir

Didanosine[1] dose (mg)/Method of administration[2]	**Tenofovir Method of administration[2]**	**N**	**% Difference (90 % CI) vs. Didanosine 400 mg alone, Fasted[3]**	
			Cmax	**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 section 4.4 regarding use of didanosine with Tenofovir.

2. Administration with food was with a light meal (~373 kcal, 20 % fat).

3. Increase = ↑; Decrease = ↓; No Effect = ⇔.

4. Includes 4 subjects weighing < 60 kg receiving ddI 250 mg.

Medicine interactions

When administered with tenofovir, C_{max} and AUC of didanosine, administered as either the buffered or enteric-coated formulation, increased significantly (see Table 3). 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 Tenofovir. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg.

When co-administered, tenofovir 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 tenofovir should be under fasted conditions. **Co-administration of tenofovir 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 tenofovir is primarily eliminated by the kidneys, co-administration of tenofovir with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir 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 tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.

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

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

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

Tenofovir should be avoided with concurrent or recent use of a nephrotoxic medicine (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 tenofovir. 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

The safety of VIRONETO in pregnancy and lactation has not been established (see section 4.3).

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIRONETO should not be used 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. 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 VIRONETO** (see section 4.3).

Fertility

There is no information on fertility with VIRONETO.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving tenofovir disoproxil (see section 4.4).

HIV-1: Approximately one third of patients are expected to experience adverse reactions following treatment with tenofovir disoproxil in combination with other antiretroviral medicines. These reactions are usually mild to moderate gastrointestinal events. Approximately 1 % of tenofovir disoproxil-treated patients discontinued treatment due to the gastrointestinal events. Co-administration of tenofovir and didanosine is not recommended as this increases adverse reactions (see section 4.5). Less frequently, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).

Hepatitis B: Approximately one quarter of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil, most of which are mild. In clinical trials of HBV infected patients, the most frequently occurring adverse reaction to tenofovir disoproxil was nausea (5,4 %).

Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy (see section 4.4).

b. Tabulated summary of adverse reactions

The following adverse reactions were associated with tenofovir disoproxil based on clinical study and post-marketing experience.

System organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Frequency unknown	Allergic reactions
Metabolism and nutrition disorders	Frequent	Hypophosphataemia[1]
	Less frequent	Hypokalaemia, lactic acidosis
Nervous system disorders	Frequent	Dizziness , insomnia headache
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, nausea, abdominal pain, flatulence , abdominal distension
	Less frequent	Increased amylase , pancreatitis
Hepato-biliary disorders	Frequent	Increased liver enzymes (ALT, AST, gamma GT)
	Less frequent	Hepatic steatosis , hepatitis

System organ class	Frequency	Adverse reaction
Skin and subcutaneous tissue disorders	Frequent	Pruritus , rash
	Less frequent	Angioedema
Musculoskeletal and connective tissue disorders	Less frequent	Rhabdomyolysis[1], muscular weakness[1], osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1, 2], myopathy[1]
Renal and urinary disorders	Less frequent	Renal insufficiency, increased creatinine, proximal renal tubulopathy (including Fanconi syndrome), acute renal failure, renal failure, acute tubular necrosis, nephrogenic diabetes insipidus, proteinuria, nephritis (including acute interstitial nephritis), polyuria.
General disorders and administration site conditions	Frequent	Asthenia , pyrexia , fatigue

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[2] This adverse reaction was identified through post-marketing surveillance

c. Description of selected adverse reactions

HIV-1 and hepatitis B

Renal impairment

As tenofovir disoproxil may cause renal damage, monitoring of renal function is recommended (see sections 4.4). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation.

However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

HIV-1

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported. The frequency of this is unknown (see section 4.4).

Hepatitis B

Exacerbations of hepatitis during treatment

In studies with nucleoside-naïve patients, on-treatment ALT elevations > 10 times ULN (upper limit of normal) and > 2 times baseline occurred in 2,6 % of tenofovir disoproxil-treated patients. Most cases were associated with a ≥ 2 log10 copies/ml reduction in viral load that preceded or coincided with the ALT elevation. Periodic monitoring of hepatic function is recommended during treatment (see section 4.4).

Exacerbations of hepatitis after discontinuation of treatment

In HBV-infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section 4.4).

Paediatric population

HIV-1 therapy

The adverse reactions in paediatric patients who received tenofovir disoproxil were consistent with those in clinical studies of tenofovir disoproxil in adults.

Reductions in bone mineral density (BMD) have been reported in paediatric patients. In HIV-infected adolescents, the BMD Z-scores in subjects who received tenofovir disoproxil were lower than those in subjects who received placebo. In HIV-infected children, the BMD Z-scores in subjects who switched to tenofovir disoproxil were lower than those in subjects who remained on regimens containing stavudine or zidovudine (see section 4.4).

In one study, 4 out of 89 paediatric patients treated with tenofovir disoproxil (median tenofovir disoproxil treatment 312 weeks) discontinued due to adverse reactions consistent with proximal renal tubulopathy.

Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 ml/minute/1,73 m^2. Among them, two patients had a clinically meaningful decline in estimated GFR which improved after discontinuation of tenofovir disoproxil.

Pre-exposure prophylaxis

Tenofovir is not indicated for PrEP in children. No safety data are available in adolescents.

Chronic hepatitis B

The adverse reactions in adolescent patients who received treatment with tenofovir disoproxil were consistent with those in clinical studies of tenofovir disoproxil in adults.

Bone mineral density (BMD) declined in HBV infected adolescents. The BMD Z-scores in subjects who received tenofovir disoproxil were lower than those in subjects who received placebo (see section 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

Symptoms

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

Management

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary.

Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/minute. It is not known whether tenofovir can be removed by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 – Antimicrobial (chemotherapeutic) agents. Antiviral agents.

Pharmacotherapeutic group: Nucleoside and nucleotide reverse transcriptase

inhibitors, ATC code: J05AF07.

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 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 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-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.

Amended text as per Clinical recommendation

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.

Special populations

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. 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 section 4.3).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Film coat

Hypromellose

Macrogol/PEG

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C. Protect from moisture.

Keep in original package until required for use.

6.5 Nature and contents of container

Al/Al cold form blisters containing 10 tablets. 3 blister cards per cardboard box.

Round, white opaque HDPE bottle, with white opaque polypropylene screw cap with induction sealed liner and containing a silica gel sachet as desiccant.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma (SA) Pty Ltd

106 16th Road

Building 2

Midrand

8 REGISTRATION NUMBER

53/20.2.8/0106

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 April 2023

10 DATE OF REVISION OF THE TEXT