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APPROVED PROFESSIONAL INFORMATION JUNE 2020

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RIOVEX 300 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Tenofovir disoproxil fumarate 300 mg which is equivalent to 245 mg tenofovir disoproxil.

Contains sugar (208,95 mg lactose monohydrate).

Excipients:

For a full list of excipients, see section 6.1

WARNING:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF RIOVEX 300 OR IN COMBINATION WITH OTHER RETROVIRALS (SEE SECTION 4.4).

RIOVEX 300 IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND SAFETY AND EFFICACY OF RIOVEX 300 HAS NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE COINFECTED WITH HBV AND HIV AND HAVE DISCONTINUED RIOVEX 300. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE RIOVEX 300 AND ARE COINFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTIHEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue coloured, oval shaped, biconvex film-coated tablets debossed with “CL 77” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RIOVEX 300 is indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection.

4.2 Posology and method of administration

Therapy with RIOVEX 300 should be initiated by a medical practitioner experienced in the management of HIV infection.

Posology

Adults:

The dose of **RIOVEX 300** is 300 mg once daily.

Dose adjustment for renal impairment:

Significantly increased medicine exposure may occur when RIOVEX 300 is administered to patients with moderate to severe renal impairment (see Section 4.3).

The pharmacokinetics of **RIOVEX 30**0 have not been evaluated in non-haemodialysis patients with creatinine clearance < 10 mL/min; therefore, no dosing recommendation is available for these patients.

It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with **RIOVEX 300**. 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 **RIOVEX 300**, and periodically during **RIOVEX 300** 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:

RIOVEX 300 should be taken orally, without regard to food.

4.3 Contraindications

RIOVEX 300 is contraindicated in:

- Patients with hypersensitivity to tenofovir or to any of the excipients listed in section 6.1.
- Patients with moderate to severe renal impairment.
- Pregnancy and lactation (see **Section 4.6**).

RIOVEX 300 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 disoproxil fumarate, since it is an ingredient of these products.

4.4 Special warnings and precautions for use

There are no study results demonstrating the effect of tenofovir as in **RIOVEX 300** 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 **RIOVEX 300** alone, or in combination with other antiretroviral. 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 **RIOVEX 300** 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 **RIOVEX 300** 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 **RIOVEX 300** 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 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 **RIOVEX 300** to patients with known risk factors for liver disease. Treatment with **RIOVEX 300** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Renal impairment

Tenofovir as in **RIOVEX 300** is principally eliminated by the kidney. **No safety data are available in patients with renal dysfunction who received RIOVEX 300 using this dosing guideline**.

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 tenofovir as in **RIOVEX 300.**

RIOVEX 300 should be avoided with concurrent or recent use of a nephrotoxic medicine. Patients at risk of, or with a history of renal dysfunction and patients receiving concomitant nephrotoxic medicines should be carefully monitored for changes in serum creatinine and phosphorus.

Patients with HIV & Hepatitis B virus Co-infection:

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk of 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 **RIOVEX 300** 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 **RIOVEX 300** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Triple nucleoside therapy:

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil fumarate as in **RIOVEX 300**, was combined with lamivudine and abacavir as well as lamivudine and didanosine as a once daily regimen.

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. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipidaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is not known. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in cases of relevant sign and symptoms.

Medicine Interactions (See **Section 4.5**)

When administered with **RIOVEX 300,** C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increases significantly (see Table 3). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy (see **Section 4.5**).

In adults weighing > 60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with **RIOVEX 300**. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg. When co-administered, **RIOVEX 300** 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 **RIOVEX 300** should be under fasted conditions. **Co-administration of RIOVEX 300 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 as in **RIOVEX 300** is primarily eliminated by the kidneys, co-administration of **RIOVEX 300** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir as in **RIOVEX 300** and/or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil,

cidofovir, aciclovir, valaciclovir, ganciclovir, valganciclovir, aminoglycosides, amphotericin B, foscarnet, pentamidine, inteleukin-2 and vancomycin.

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 tenofovir disoproxil fumarate as in **RIOVEX 300** (see **Section 4.8**). Arthralgia's 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 disoproxil fumarate (see **Section 4.4**).

RIOVEX 300 decreases bone mineral density.

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. It is recommended that appropriate consultation be obtained if bone abnormalities are suspected.

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.

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, atypical mycobacterial infections, cytomegalovirus retinitis, *Pneumocystis jirovecii (carinii)* pneumonia (PCP) 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 and autoimmune hepatitis) 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.

Pancreatitis

Pancreatitis has been observed in some patients receiving **RIOVEX 300**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **RIOVEX 300** until diagnosis of pancreatitis is excluded.

Liver disease

Use of **RIOVEX 300** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **RIOVEX 300** 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 professional information 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 **RIOVEX 300** 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 **RIOVEX 300**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Paediatric Use:

Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.

Elderly Use:

In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy.

Lactose

RIOVEX 300 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 **RIOVEX 300**.

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 mediate interactions involving tenofovir with other medicines is low.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of **RIOVEX 300** 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.

Tenofovir as in **RIOVEX 300** 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 summarises pharmacokinetic effects of co-administered medicine on tenofovir as in **RIOVEX**

300 pharmacokinetics and effects of tenofovir as in **RIOVEX 300** on the pharmacokinetics of co-administered medicines.

Table 3 summarises the medicine interaction between tenofovir as in **RIOVEX 300** and didanosine. When administered with multiple doses of tenofovir as in **RIOVEX 300**, 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 as in **RIOVEX 300**, 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 as in RIOVEX 300[1] in the presence of the co-administered medicine

Co-administered Medicine	**Dose of Co-administered Medicine (mg)**	**N**	**% Change of tenofovir as in RIOVEX 300 Pharmacokinetic Parameters[2] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
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 x 14 days	29	↔	↔	↔
Saquinavir/ Ritonavir	1 000/100 twice daily x 14 days	35	↔	↔	↑ 23 (↑ 16 to ↑ 30)

1. Patients received tenofovir disoproxil fumarate 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 as in **RIOVEX 300**.

Table 2

Medicine Interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of tenofovir as in RIOVEX 300.

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	1250 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	Saquinavir/ Ritonavir	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29[7] (↑ 12 to ↑ 48)	↑ 47[7] (↑ 23 to ↑ 76)

Ritonavir	1 000/100 twice daily x 14 days		↔	↔	↑ 23 (↑ 3 to ↑ 46)

1. Increase = ↑; Decrease = ↓; No Effect = ↔; NA = Not Applicable
2. Atazanavir Prescribing Information.
3. In HIV-infected patients, addition of tenofovir disoproxil fumarate 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 **RIOVEX 300**. 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. Ethinylestradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with **RIOVEX 300**.
7. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir disoproxil fumarate and ritonavir-boosted saquinavir are co- administered.

Table 3

Medicine Interactions: Pharmacokinetic parameters for didanosine in the presence of tenofovir as in RIOVEX 300

Didanosine[1] Dose (mg)/Method of Administration[2]	**Tenofovir as in RIOVEX 300 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)

See **section 4.4** regarding use of didanosine with tenofovir as in **RIOVEX 300**.

1. Administration with food was with a light meal (~373 kcal, 20 % fat).
2. Increase = ↑; Decrease = ↓; No Difference = ↔.
3. Includes 4 subjects weighing < 60 kg receiving ddI 250 mg.

Medicine interactions

When administered with tenofovir as in **RIOVEX 300**, 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 **RIOVEX 300**. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg.

When co-administered, **RIOVEX 300** 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 **RIOVEX 300** should be under fasted conditions. **Co-administration of RIOVEX 300 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 as in **RIOVEX 300** is primarily eliminated by the kidneys, co-administration of **RIOVEX 300** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir as in **RIOVEX 300** and/or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides, amphotericin B, foscarnet, pentamidine, inteleukin-2 and vancomycin.

Higher **RIOVEX 300** concentrations could potentiate **RIOVEX 300-**associated adverse events, including renal disorders.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir as in **RIOVEX 300** concentrations. The mechanism of this interaction is unknown. **Patients receiving atazanavir and lopinavir/ritonavir and RIOVEX 300 should be monitored for tenofovir -associated adverse events. RIOVEX 300 should be discontinued in patients who develop tenofovir-associated adverse events.**

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

RIOVEX 300 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 **RIOVEX 300**. 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

Safety 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, **RIOVEX 300** should not be used during pregnancy (see **Section 4.3**).

Late onset neurological disorders relating to mitochondrial dysfunction have been observed in children who have been exposed in utero and/or postnatally to nucleoside analogues as contained in **RIOVEX 300**.

Breastfeeding

Tenofovir is secreted in human milk. (see **Section 4.3**).

It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV to the infant.

Fertility

There are limited clinical data with respect to the effect of **RIOVEX 300** on fertility. Animal studies do not indicate harmful effects of **RIOVEX 300** on fertility.

4.7 Effects on ability to drive and use machines

RIOVEX 300 may cause dizziness. Patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that **RIOVEX 300** does not adversely affect their ability to do so.

4.8 Undesirable effects

Immune system disorders:

Frequency unknown: Allergic reaction (including angioedema), immune reconstitution inflammatory syndrome.

Metabolism and nutrition disorders:

Less frequent: Lactic acidosis, including fatal cases, usually associated with severe hepatomegaly and steatosis.

Frequency unknown: Hypophosphataemia, hypokalemia, fat redistribution, lipodystrophy, hypertriglyceridaemia, weight loss.

Psychiatric disorders:

Frequent: Anxiety, depression, insomnia.

Nervous system disorders:

Frequent: Dizziness, headache.

Less frequent: Peripheral neuropathy (includes peripheral neuritis and neuropathy), convulsions.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Dyspnoea, pneumonia, chest pain.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, flatulence.

Frequency unknown: Abdominal pain, raised serum-amylase concentrations, pancreatitis, dyspepsia.

Hepato-biliary disorders:

Frequency unknown: Increased liver enzymes (alanine aminotransferase, aspartate transaminase, gamma-glutamyltransferase), hepatitis, hepatic steatosis, hepatoxicity.

Skin and subcutaneous tissue disorders:

Frequent: Skin rashes

Less frequent: Sweating.

Frequency unknown: Pruritus.

Musculoskeletal, connective tissue disorders and bone disorders:

Less frequent: Myalgia and arthralgia.

Frequency unknown: Myopathy, osteomalacia (both associated with proximal renal tubulopathy), rhabdomyolysis, muscular weakness, bone abnormalities, back pain, osteonecrosis.

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:

Frequent: Asthenia

Frequency unknown: Pyrexia.

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 via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

In overdose, side effects can be precipitated and/or be of increased severity.

Management

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.2.8 Antiviral agents.

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 medicines. In treatment-naïve patients treated with tenofovir disoproxil fumarate + lamivudine + efavirenz, viral isolates from (17 %) patients with virologic failure showed reduced susceptibility to tenofovir.

In treatment-experienced patients, (4,6 %) of the tenofovir disoproxil fumarate-treated patients with virologic 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 substitution selected by tenofovir is also selected in some HIV-1-infected subjects treated with abacavir, didanosine, or zalcitabine. HIV-1 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

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 disoproxil fumarate 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 disoproxil fumarate 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 and elimination

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.

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 (Table 4). 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**).

Table 4: Pharmacokinetic Parameters (Mean ± SD) of Tenofovir in Subjects with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	> 80 (N=3)	50-80 (N=10)	30-49 (N=8)	12-29 (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

* 300 mg, single dose of tenofovir disoproxil fumarate

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

5.3 Preclinical safety data

Non-clinical safety pharmacology studies reveal no special hazard for humans. Findings in repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40 fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

Genotoxicity studies revealed positive results in the *in vitro* mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes. However, it was negative in an *in vivo* mouse bone marrow micronucleus assay.

Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

Reproductive studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch. The tablets are coated with coating made up of hydroxypropyl methylcellulose, indigo carmine aluminum lake, lactose monohydrate, titanium dioxide, triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light and moisture.

Keep in original packaging until required for use.

Keep the bottle tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

HDPE container

Tablets are packed in a 75 mL round white HDPE container with 38 - 400 mm neck finish, closed with either a white 38 mm child resistant closure with pulp and heat seal liner or a white 38 mm continuous thread closure with pulp and heat seal liner, packed in an outer carton. Each HDPE container contains a 3 g silica gel sachet.

Pack sizes include 28 or 30 tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

46/20.2.8/0852

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/07/2020

10. DATE OF REVISION OF THE TEXT

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