PROFESSIONAL INFORMATION LEAFLET

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE

RICOVIR (300 mg, film-coated tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each RICOVIR film-coated tablet contains 300 mg of tenofovir disoproxil fumarate

Contains sugar:

Lactose monohydrate 574,00 mg

WARNING:

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 RICOVIR 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 RICOVIR. 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 RICOVIR. IF APPROPRIATE, RESUMPTION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE *SECTION 4.4*).

3 PHARMACEUTICAL FORM

Light blue coloured, round, biconvex, film-coated tablets, debossed with '153' on one side and 'M' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

HIV-1 infection

- RICOVIR 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 in treatment-naïve adults and in treatment-experienced adults.

Chronic Hepatitis B

RICOVIR 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 RICOVIR 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

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

Adults

For the treatment of HIV-1 or chronic hepatitis B in adults:

The dose of RICOVIR (tenofovir disoproxil fumarate) is 300 mg once daily taken orally, without regard to food.

Chronic Hepatitis B

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

Special populations

Dose Adjustment for Renal Impairment:

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

Significantly increased exposure occurs when RICOVIR is administered to patients with moderate to severe renal impairment (see *section 4.3*).

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

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).

Elderly population:

No data are available on which to make a dose recommendation for patients over the age of 65 years.

Children and adolescents:

Chronic Hepatitis B

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

Method of administration

For oral use.

4.3 Contraindications

- RICOVIR is contra-indicated in patients with previously demonstrated hypersensitivity to any of the components of the product.
- Uncontrolled renal failure (see *section 4.4*).
- Pregnancy and lactation (see *section 4.6*).
- Patients younger than 18 years of age.
- RICOVIR 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.

4.4 Special warnings and precautions for use

Patients to be treated with RICOVIR 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 RICOVIR on clinical progression of HIV-1.

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 RICOVIR was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen.

Renal impairment:

- RICOVIR is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of RICOVIR with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of RICOVIR and/or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.
- RICOVIR is not recommended for patients with creatinine clearance < 50 ml/min or patients who require haemodialysis.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) has been reported with the use of tenofovir disoproxil fumarate in clinical practice. Careful monitoring of renal function (serum creatinine and serum phosphate) is therefore recommended before taking RICOVIR.

***K65R mutation*:**

- RICOVIR should be avoided in antiretroviral experienced patients with HIV-1 harbouring the K65R mutation.

Bone mineral density:

- Decreases in bone mineral density of spine and changes in bone biomarkers from baseline are significantly greater with tenofovir disoproxil fumarate (RICOVIR).
- Decreases in bone mineral density of the hip are significantly greater.
- Clinically relevant bone fractures are reported.
- If bone abnormalities are suspected, then appropriate consultation should be obtained.
- Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk of osteopenia.

Bone Effects:

- 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.
- 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 RICOVIR (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 products containing tenofovir DF (see *section 4.4*).

Patients with HIV and hepatitis B or C virus co-infection:

- Patients with chronic hepatitis B or C 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 RICOVIR 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 RICOVIR therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Liver disease:

- Use of RICOVIR can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of RICOVIR 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.

Exacerbations of hepatitis:

Flares on treatment:

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

Flares after treatment discontinuation:

- Acute exacerbations of hepatitis have been reported in patients after the discontinuation of hepatitis B therapy.
- Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported.
- Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted.
- In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

Lactic acidosis and severe hepatomegaly with steatosis:

- Lactic acidosis, usually associated with hepatic steatosis, including fatal cases, has been reported with the use of nucleoside analogues, such as in RICOVIR.
- Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure.
- Lactic acidosis generally occurs after a few or several months of treatment.
- Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

- Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol).
- Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk. Patients at increased risk should be followed closely. (see section 4.4).
- 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 RICOVIR 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 RICOVIR 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

- Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

  Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.
- In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and respond as follows:

- Lactate 2-5 mmol/ℓ: monitor regularly and be alert for clinical signs.
- Lactate 5-10 mmol/ℓ without symptoms: monitor closely.

- Lactate 5-10 mmol/ℓ with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate > 10 mmol/ℓ: STOP all therapy (80 % mortality in case studies).

- The above lactate values may not be applicable to paediatric patients.
- Caution should be exercised when administering RICOVIR to patients with known risk factors for liver disease (see *section 4.4*).
- Treatment with RICOVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Mitochondrial dysfunction:

- Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage.

Interaction with didanosine:

- Co-administration of RICOVIR and didanosine is not recommended as it results in a 40-60 % increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see *section 4.5*).

Opportunistic infections:

- Patients receiving the combination, or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by doctors experienced in the treatment of patients with HIV associated diseases.
- Regular monitoring of viral load and CD4 counts needs to be done.

Transmission of HIV:

- Patients must be advised that antiretroviral therapies, including combinations with RICOVIR, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.
- Appropriate precautions must continue to be used.

Lipodystrophy and metabolic abnormalities:

- Combination antiretroviral therapy, including RICOVIR, has been associated with the redistribution of body fat (lipodystrophy) 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. The long-term consequences of these events are unknown. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.
- A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances.
- Clinical examination should include evaluation for physical signs of fat redistribution.
- Consideration should be given to the measurement of fasting serum lipids and blood glucose.
- Lipid disorders should be managed as clinically appropriate.

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.

Osteonecrosis:

- Although the etiology 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.

Pancreatitis:

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

Lactose warning:

- RICOVIR contains lactose monohydrate may have an effect on the glycaemic control of patients with diabetes mellitus.

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

Geriatric use:

- Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Paediatric population:

- Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.
- There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally 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 unknown.
- 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 case of relevant signs or symptoms**.**

4.5 Interaction with other medicines and other forms of Interaction

Interaction studies have only been performed in adults.

***Concomitant antiretroviral medicinal products*:**

- At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro substance 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 RICOVIR with other medicinal products is low.
- Emtricitabine, lamivudine, indinavir, efavirenz, nelfinavir, and saquinavir (ritonavir boosted): co-administration with tenofovir disoproxil fumarate did not result in any clinically relevant interaction.
- When tenofovir disoproxil fumarate was administered with lopinavir/ritonavir, no changes were observed in the pharmacokinetics of lopinavir and ritonavir. Tenofovir AUC was increased by approximately 30 % when tenofovir disoproxil fumarate was administered with lopinavir/ritonavir. Higher tenofovir concentrations could potentiate tenofovir associated adverse events, including renal disorders.
- When didanosine gastro-resistant capsules were administered 2 hours prior to or concurrently with tenofovir disoproxil fumarate, the AUC for didanosine was on average increased by 48 % and 60 % respectively. The mean increase in the AUC of didanosine was 44 % when the buffered tablets were administered 1 hour prior to tenofovir. In both cases the pharmacokinetic parameters for tenofovir administered with a light meal were unchanged. The co-administration of tenofovir disoproxil fumarate and didanosine is not recommended (see *section 4.4*).
- When tenofovir disoproxil fumarate was administered with atazanavir, a decrease in concentrations of atazanavir was observed (decrease of 25 % and 40 % of AUC and C_{min} respectively compared to atazanavir 400 mg). When ritonavir was added to atazanavir, the negative impact of tenofovir on atazanavir C_{min} was significantly reduced, whereas the decrease of AUC was of the same magnitude (decrease of 25 % and 26 % of AUC and C_{min} respectively compared to atazanavir/ritonavir 300/100 mg). The co-administration of

atazanavir/ritonavir with tenofovir resulted in increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. The co-administration of atazanavir with ritonavir in combination with tenofovir has been substantiated in a clinical study.

Other interactions:

- Co-administration of tenofovir disoproxil fumarate, methadone, ribavirin, rifampicin, adefovir dipivoxil or the hormonal contraceptive norgestimate/ethinyl oestradiol did not result in any pharmacokinetic interaction.

- Tenofovir is excreted renally, both by filtration and active secretion via the human organic anion transporter 1 (hOAT1). Co-administration of tenofovir disoproxil fumarate with other medicinal products that are also actively secreted via the anion transporter (e.g. cidofovir) may result in increased concentrations of tenofovir or of the co-administered medicinal product.
- RICOVIR 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 RICOVIR. 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

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

Insufficient data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

However, RICOVIR should not be used during pregnancy.

Breastfeeding

It is not known whether tenofovir is excreted in human milk.

Tenofovir as contained in RICOVIR, is shown to be secreted in the milk of rats.

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 tenofovir disoproxil on fertility. Animal studies do not indicate harmful effects of tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	**Less frequent**	**Frequency not known**
Blood and the lymphatic system disorders:			neutropenia
Immune system disorders:		angioedema, allergic reaction	
Metabolism and nutrition disorders:	hypophosphataemia	hypokalaemia, lactic acidosis, lipodystrophy, weight loss, fat redistribution	
Psychiatric disorders:		depression	
Nervous system disorders:	dizziness, headache	insomnia, peripheral neuropathy, anxiety	
Respiratory, thoracic and mediastinal disorders:		dyspnoea, pneumonia	
Gastrointestinal disorders:	diarrhoea, nausea, vomiting, abdominal pain, abdominal distension, flatulence	pancreatitis, anorexia, increased amylase	
Hepato-biliary disorders:	increased transaminases	hepatic steatosis, hepatitis	
Skin and subcutaneous tissue disorders:	rash, sweating		
Musculoskeletal, connective tissue and bone disorders:		rhabdomyolysis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy, arthralgia, myalgia, back pain	

Renal and urinary disorders:		increased creatinine, acute renal failure, renal failure, acute tubular necrosis, proximal renal tubulopathy (including Fanconi syndrome), nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus	
General disorders and administrative site conditions:		asthenia, fatigue, fever, chest pain	

Safety and effectiveness of RICOVIR in paediatric patients younger than 18 years of age or less than 35 kg with chronic hepatitis B have not been established.

Description of selected adverse reactions

HIV-1 and hepatitis B:

Renal impairment

As RICOVIR may cause renal damage monitoring of renal function is recommended (see *sections 4.4*). Proximal renal tubulopathy generally resolved or improved after RICOVIR 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 experiencing incomplete recovery of renal function despite RICOVIR discontinuation (see *section 4.4*).

Lactic acidosis

Cases of lactic acidosis have been reported with tenofovir disoproxil (as contained in RICOVIR) alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during RICOVIR treatment, including fatal outcomes.

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 cART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see *section 4.4*).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to cART. The frequency of this is unknown (see *section 4.4*).

Hepatitis B:

Exacerbations of hepatitis during treatment

Periodic monitoring of hepatic function is recommended during treatment (see *section 4.4*).

Exacerbations of hepatitis after discontinuation of treatment

In HBV infected patients, exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see *section 4.4*).

Other special populations

Patients with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in adult patients with renal impairment treated with RICOVIR (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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "Report Drug Reaction Process", found online under SAHPRA's safety publications: https://www.sahpra.org.za/

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see *section 4.8)*. Limited clinical experience at doses higher than the therapeutic dose is available.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; nucleoside and nucleotide reverse transcriptase inhibitors, ATC code: J05AF07

Mechanism of action:

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate and is converted *in vivo* to tenofovir.

Pharmacodynamic effects:

It is a nucleoside reverse transcriptase inhibitor.

Tenofovir is phosphorylated by cellular enzymes to form tenofovir diphosphate.

Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase, by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation in DNA, by chain termination.

Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

Resistance:

Strains of HIV-1 with reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected *in vitro* and, in some patients, treated with tenofovir in combination with certain antiretroviral agents.

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

In treatment-experienced patients, 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 can also be selected by abacavir, didanosine or zalcitabine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir.

Tenofovir disoproxil fumarate should be avoided in antiretroviral experienced patients with strains harbouring the K65R mutation.

Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate.

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

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

Absorption:



Tenofovir disoproxil fumarate is a water soluble diester prodrug 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 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 2287 ± 685 ng*h/ml, respectively.
The pharmacokinetics of tenofovir are dose proportional over a dose range of 75 to 600 mg and are not affected by repeated dosing.

Effects of Food on Oral Absorption:
Administration of tenofovir disoproxil fumarate with a high fat meal (~700 to 1000 kcal containing 40 to 50 % fat) enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40 % and C_{max} by approximately 14 %.

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 substance.

Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ± 119 ng/ml and 3324 ± 1370 ng*h/ml following multiple doses of tenofovir 300 mg once daily in the fed state, when meal content was not controlled.

Distribution:
In vitro protein binding of tenofovir to human plasma or serum protein 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 have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes.

Elimination

Following IV administration of tenofovir, approximately 70-80 % of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours.

After multiple oral doses of tenofovir 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:

Renal impairment

Tenofovir pharmacokinetics 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 increased. It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance < 50 ml/min or in patients with ESRD who require dialysis (see *section 4.2*).

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

Hepatic impairment

Tenofovir pharmacokinetics after 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. Change in tenofovir dosing is not required in patients with hepatic impairment.

Paediatric and Elderly patients

Pharmacokinetic studies have not been performed in children (<18 years) or in the elderly (> 65 years).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Film-coating

Hypromellose,

Titanium dioxide,

Triacetin /glycerol triacetate,

FD & C Blue #2/Indigo carmine aluminium lake

Lactose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container. Protect from light.

Do not use if seal over bottle opening is broken or missing.

Do not remove from carton until required for use.

6.5 Nature and contents of container

RICOVIR film-coated tablets are supplied as follows:

HDPE bottle of 30's and HDPE bottle of 100's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street,

Isando, Gauteng,

1601

8 REGISTRATION NUMBER(S)

45/20.2.28/0825

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2012

10 DATE OF REVISION OF TEXT

12 September 2022