

1. Name of The Medicinal Product

RICOVIR-EM

Emtricitabine/Tenofovir disoproxil fumarate 200 mg/300 mg Tablets

2. Qualitative and Quantitative Composition

Each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir).

Excipients with known effects:

Each tablet contains 136 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Blue-coloured, oval-shaped, film-coated tablets debossed with "M117" on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of HIV-1 infection:

Emtricitabine and Tenofovir disoproxil fumarate is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults. The following points should be considered when initiating therapy with Emtricitabine and Tenofovir disoproxil fumarate for the treatment of HIV-1 infection:

- It is not recommended that Emtricitabine and Tenofovir disoproxil fumarate be used as a component of a triple nucleoside regimen.
- Emtricitabine and Tenofovir disoproxil fumarate should not be co-administered with lamivudine + tenofovir DF + Efavirenz, emtricitabine, tenofovir DF or lamivudine-containing products.

In treatment experienced patients, the use of Emtricitabine and Tenofovir disoproxil fumarate should be guided by laboratory testing and treatment history.

Pre-exposure prophylaxis (PrEP):

Emtricitabine/Tenofovir Disoproxil is indicated in combination with safer sex practices for pre exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

When prescribing TENOF-EM for PrEP, healthcare providers must:

- prescribe TENOF-EM as part of a comprehensive prevention strategy because emtricitabine/tenofovir disoproxil is not always effective in preventing the acquisition of HIV-1 infection.
- counsel all uninfected individuals to strictly adhere to the recommended TENOF-EM dosing schedule because the effectiveness of emtricitabine/tenofovir disoproxil in reducing the risk of acquiring HIV-1 was strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials.
- confirm a negative HIV-1 test immediately prior to initiating TENOF-EM for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status, including acute or primary HIV-1 infection; and - screen for HIV-1 infection at least once every 3 months while taking emtricitabine/tenofovir disoproxil for PrEP.

4.2 Posology and method of administration

RICOVIR-EM should be initiated by a physician experienced in the management of HIV infection.

Posology

Treatment of HIV-1 infection:

The dosage of Emtricitabine and Tenofovir disoproxil fumarate is one tablet once daily taken orally with or without food.

Dose adjustment for renal impairment

Significantly increased drug exposures occurred when emtricitabine or tenofovir DF were administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of Emtricitabine and Tenofovir disoproxil fumarate should be adjusted in patients with baseline creatinine clearance of 30-49 mL/min using the recommendations in below Table. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients.

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance of 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment.

Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)		
	≥ 50	30-49	<30 (including patients requiring hemodialysis)
Recommended Dosing Interval	Every 24 hours	Every 48 hours	Emtricitabine and Tenofovir Disoproxil fumarate Should not be administered

a Calculated using ideal (lean) body weight

Pre-exposure prophylaxis (PrEP):

This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

Posology

Prevention of HIV in adults: One tablet, once daily.

Adults with renal impairment

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment.

TENOF-EM should only be used in individuals with creatinine clearance (CrCl) < 80 mL/min if the potential benefits are considered to outweigh the potential risks. See Table 1.

Table 1: Dosing recommendations in adults with renal impairment

	Pre-exposure prophylaxis
Mild renal impairment (CrCl 50-80mL/min)	Limited data from clinical studies support once daily dosing in HIV-1 uninfected individuals with CrCl 60-80 mL/min. Use is not recommended in HIV-1 uninfected individuals with CrCl < 60 mL/min as it has not been studied in this population

Moderate renal impairment (CrCl 30-49 mL/min)	Not recommended for use in this population.
Severe renal impairment (CrCl < 30 mL/min) and haemodialysis patients.	Not recommended for use in this population.

Method of administration

Oral administration. It is preferable that RICOVIR-EM is taken with food.

The film-coated tablet can be disintegrated in approximately 100 mL of water, orange juice or grape juice and taken immediately.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Use for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status.

4.4 Special warnings and precautions for use

Patients with HIV-1 harbouring mutations

RICOVIR-EM should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1).

Overall HIV-1 infection prevention strategy

RICOVIR-EM is not always effective in preventing the acquisition of HIV-1. The time to onset of protection after commencing RICOVIR-EM is unknown.

RICOVIR-EM should only be used for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (e.g. consistent and correct condom use, knowledge of HIV-1 status, regular testing for other sexually transmitted infections).

Risk of resistance with undetected HIV-1 infection:

RICOVIR-EM should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative (see section 4.3). Individuals should be re-confirmed to be HIV-negative at frequent intervals (e.g. at least every 3 months) using a combined antigen/antibody test while taking RICOVIR-EM for pre-exposure prophylaxis.

RICOVIR-EM alone does not constitute a complete regimen for the treatment of HIV-1 and HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who are only taking RICOVIR-EM.

If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, use of RICOVIR-EM should be delayed for at least one month and HIV-1 status reconfirmed before starting RICOVIR-EM for pre-exposure prophylaxis.

Importance of adherence:

HIV-1 uninfected individuals should be counselled at frequent intervals to strictly adhere to the recommended RICOVIR-EM daily dosing schedule.

Patients with hepatitis B or C virus infection

HIV-1 infected patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Physicians should refer to current HIV treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV).

The safety and efficacy of RICOVIR-EM for pre-exposure prophylaxis in patients with HBV or HCV infection has not been established.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products. See also under *Use with ledipasvir and sofosbuvir or sofosbuvir and velpatasvir* below.

Tenofovir disoproxil is indicated for the treatment of HBV and emtricitabine has shown activity against HBV in pharmacodynamic studies but the safety and efficacy of RICOVIR-EM have not been specifically established in patients with chronic HBV infection.

Discontinuation of RICOVIR-EM therapy in patients infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue RICOVIR-EM should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. 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 disease

The safety and efficacy of RICOVIR-EM have not been established in patients with significant underlying liver disorders. The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment and no dose adjustment is required. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for RICOVIR-EM in patients with hepatic impairment (see sections 4.2 and 5.2).

HIV-1 infected patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal and bone effects in adults

Renal effects

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil (see section 4.8).

Renal monitoring

Prior to initiating RICOVIR-EM for the treatment of HIV-1 infection or for use in pre-exposure prophylaxis, it is recommended that creatinine clearance is calculated in all individuals.

In individuals without risk factors for renal disease, it is recommended that renal function (creatinine clearance and serum phosphate) is monitored after two to four weeks of use, after three months of use and every three to six

months thereafter.

In individuals at risk for renal disease more frequent monitoring of renal function is required.

See also under Co-administration of other medicinal products below.

Renal management in HIV-1 infected patients

If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 50 mL/min in any patient receiving RICOVIR-EM, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Consideration should be given to interrupting treatment with RICOVIR-EM in patients with creatinine clearance decreased to < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with RICOVIR-EM should also be considered in case of progressive decline of renal function when no other cause has been identified.

A careful benefit-risk assessment is needed when RICOVIR-EM is used in patients with creatinine clearance < 60 mL/min, and renal function should be closely monitored. In addition, the clinical response to treatment should be closely monitored in patients receiving RICOVIR-EM at a prolonged dosing interval. The use of RICOVIR-EM is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in patients who require haemodialysis since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

Renal management in pre-exposure prophylaxis

RICOVIR-EM has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population. If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 60 mL/min in any individual receiving RICOVIR-EM for pre-exposure prophylaxis, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Consideration should be given to interrupting use of RICOVIR-EM in individuals with creatinine clearance decreased to < 60 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting use of RICOVIR-EM should also be considered in case of progressive decline of renal function when no other cause has been identified.

Bone effects

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8).

Tenofovir disoproxil may also cause a reduction in bone mineral density (BMD).

If bone abnormalities are suspected or detected then appropriate consultation should be obtained.

Treatment of HIV-1 infection

In view of the bone abnormalities associated with tenofovir disoproxil, alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.

Renal and bone effects in the paediatric population

There are uncertainties associated with the long-term renal and bone effects of tenofovir disoproxil during the treatment of HIV-1 infection in the paediatric population and the long-term renal and bone effects of RICOVIR-EM when used for pre-exposure prophylaxis in uninfected adolescents (see section 5.1). Moreover, the reversibility of

renal toxicity after cessation of tenofovir disoproxil for treatment of HIV-1 or after cessation of RICOVIR-EM for pre-exposure prophylaxis cannot be fully ascertained.

A multidisciplinary approach is recommended to weigh the benefit/risk balance of the use of RICOVIR-EM for the treatment of HIV-1 infection or for pre-exposure prophylaxis, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation on a case by case basis.

When using RICOVIR-EM for pre-exposure prophylaxis individuals should be reassessed at each visit to ascertain whether they remain at high risk of HIV-1 infection. The risk of HIV-1 infection should be balanced against the potential for renal and bone effects with long-term use of RICOVIR-EM.

Renal monitoring

Renal function (creatinine clearance and serum phosphate) should be evaluated prior to initiating RICOVIR-EM for treatment of HIV-1 or for pre-exposure prophylaxis, and should be monitored during use as in adults (see above).

Renal management

If serum phosphate is confirmed to be < 3.0 mg/dL (0.96 mmol/L) in any paediatric patient receiving RICOVIR-EM, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of RICOVIR-EM use. Interrupting use of RICOVIR-EM should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity

The same recommendations apply as in adults (see Co-administration of other medicinal products below).

Renal impairment

The use of RICOVIR-EM is not recommended in individuals under the age of 18 years with renal impairment (see section 4.2). RICOVIR-EM should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during RICOVIR-EM use.

Bone effects

Use of tenofovir disoproxil may cause a reduction in BMD. The effects of tenofovir disoproxil-associated changes in BMD on long-term bone health and future fracture risk are uncertain (see section 5.1).

If bone abnormalities are detected or suspected during use of RICOVIR-EM in any paediatric patient, consultation with an endocrinologist and/or nephrologist should be obtained.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure *in utero*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

HIV-1 infected patients receiving RICOVIR-EM 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 physicians experienced in the treatment of patients with HIV associated diseases.

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 CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Co-administration of other medicinal products

Use of RICOVIR-EM should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see section 4.5). If concomitant use with nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in HIV-1 infected patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If RICOVIR-EM is co-administered with an NSAID, renal function should be monitored adequately.

A higher risk of renal impairment has been reported in HIV-1 infected patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease inhibitor. Close monitoring of renal function is required in these patients (see section 4.5). In HIV-1 infected patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.

RICOVIR-EM should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide, or other cytidine analogues, such as lamivudine (see section 4.5).

RICOVIR-EM should not be administered concomitantly with adefovir dipivoxil.

Use with ledipasvir and sofosbuvir, sofosbuvir and velpatasvir or sofosbuvir, velpatasvir and voxilaprevir

Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat).

The safety of tenofovir disoproxil when co-administered with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

Co-administration of tenofovir disoproxil and didanosine

Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.5).

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage in HIV-1 infected patients when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. There is close structural similarity between lamivudine and emtricitabine and similarities in the pharmacokinetics and pharmacodynamics of these two agents. Therefore, the same problems may be seen if RICOVIR-EM is administered with a third nucleoside analogue.

Elderly

RICOVIR-EM has not been studied in individuals over the age of 65 years. Individuals over the age of 65 years are more likely to have decreased renal function, therefore caution should be exercised when administering RICOVIR-EM to older people.

Excipients

RICOVIR-EM contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

As RICOVIR-EM contains emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with RICOVIR-EM.

Concomitant use not recommended

RICOVIR-EM should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide or other cytidine analogues, such as lamivudine (see section 4.4). RICOVIR-EM should not be administered concomitantly with adefovir dipivoxil.

Didanosine

The co-administration of RICOVIR-EM and didanosine is not recommended (see section 4.4 and Table 2).

Renally eliminated medicinal products

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of RICOVIR-EM with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.

Use of RICOVIR-EM should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

Other interactions

Table 2: Interactions between RICOVIR-EM or its individual component(s) and other medicinal products

Medicinal product by therapeutic areas	Recommendation concerning co-administration with RICOVIR-EM (emtricitabine 200 mg, tenofovir disoproxil 245 mg)
ANTI-INFECTIVES	
Antiretrovirals	
Protease inhibitors	
Atazanavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Atazanavir/Ritonavir/Emtricitabine	
Darunavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir/Emtricitabine	
Lopinavir/Ritonavir/Tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d./245 mg q.d.)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Lopinavir/Ritonavir/Emtricitabine	
NRTIs	
Didanosine/Tenofovir disoproxil Didanosine/Emtricitabine	Co-administration of RICOVIR-EM and didanosine is not recommended (see section 4.4). Increased systemic exposure to didanosine may increase didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the

	treatment of HIV-1 infection.
Lamivudine/Tenofovir disoproxil	Lamivudine and RICOVIR-EM should not be administered concomitantly (see section 4.4).
Efavirenz/Tenofovir disoproxil	No dose adjustment of efavirenz is required.
ANTI-INFECTIVES	
Hepatitis B virus (HBV) antiviral agents	
Adefovir dipivoxil/Tenofovir disoproxil	Adefovir dipivoxil and RICOVIR-EM should not be administered concomitantly (see section 4.4).
Hepatitis C virus (HCV) antiviral agents	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) ¹	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) ¹	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Dolutegravir (50 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	No dose adjustment is required. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.

	The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Lopinavir/Ritonavir (800 mg/200 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Raltegravir (400 mg b.i.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma concentrations of velpatasvir. Co-administration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg q.d.) ³ + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	No dose adjustment is required.
Ribavirin/Tenofovir disoproxil	No dose adjustment of ribavirin is required.

Herpes virus antiviral agents		
Famciclovir/Emtricitabine		No dose adjustment of famciclovir is required.
Antimycobacterials		
Rifampicin/Tenofovir disoproxil		No dose adjustment is required.
ORAL CONTRACEPTIVES		
Norgestimate/Ethinyl oestradiol/Tenofovir disoproxil		No dose adjustment of norgestimate/ethinyl oestradiol is required.
IMMUNOSUPPRESSANTS		
Tacrolimus/Tenofovir disoproxil/Emtricitabine		No dose adjustment of tacrolimus is required.
NARCOTIC ANALGESICS		
Methadone/Tenofovir disoproxil		No dose adjustment of methadone is required.

NC = not calculated.

N/A = not applicable.

¹ Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.

² The predominant circulating metabolite of sofosbuvir.

³ Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of RICOVIR-EM may be considered during pregnancy, if necessary.

Breast-feeding

Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore RICOVIR-EM should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

No human data on the effect of RICOVIR-EM are available. Animal studies do not indicate harmful effects of emtricitabine or tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, individuals should be informed that dizziness has been reported during treatment with both emtricitabine and tenofovir disoproxil.

4.8 Undesirable effects

Summary of the safety profile

HIV-1 infection

Description of selected adverse reactions

Renal impairment

As RICOVIR-EM may cause renal damage monitoring of renal function is recommended (see section 4.4). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some HIV-1 infected 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 experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

Lactic acidosis: Cases of lactic acidosis have been reported with tenofovir disoproxil 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 tenofovir disoproxil treatment, including fatal outcomes.

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).

Other special populations

Individuals with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any adults with renal impairment receiving RICOVIR-EM (see sections 4.2, 4.4 and 5.2). The use of RICOVIR-EM is not recommended in individuals under the age of 18 years with renal impairment (see sections 4.2 and 4.4).

Exacerbations of hepatitis after discontinuation of treatment

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

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

Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR03

Mechanism of action

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Resistance

In vitro: Resistance has been seen *in vitro* and in some HIV-1 infected patients due to the development of the M184V/I mutation with emtricitabine or the K65R mutation with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir. 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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of RICOVIR-EM to healthy subjects, emtricitabine and tenofovir disoproxil are rapidly absorbed and tenofovir disoproxil is converted to tenofovir. In order to optimise the absorption of tenofovir, it is recommended that RICOVIR-EM should preferably be taken with food.

Distribution

After oral administration of emtricitabine or tenofovir disoproxil, emtricitabine and tenofovir are widely distributed throughout the body.

Biotransformation

There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). Neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination

The elimination half-life of emtricitabine is approximately 10 hours.
The elimination half-life of tenofovir is approximately 12 to 18 hours.

Elderly

Pharmacokinetic studies have not been performed with emtricitabine or tenofovir (administered as tenofovir disoproxil) in the elderly (over 65 years of age).

Gender

Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Ethnicity

No clinically important pharmacokinetic difference due to ethnicity has been identified for emtricitabine. The pharmacokinetics of tenofovir (administered as tenofovir disoproxil) have not been specifically studied in different ethnic groups.

Paediatric population

Pharmacokinetic studies have not been performed with RICOVIR-EM in children and adolescents (under 18 years of age).

Renal impairment

The pharmacokinetics of emtricitabine and tenofovir (administered as tenofovir disoproxil) in paediatric patients with renal impairment have not been studied. No data are available to make dose recommendations (see sections 4.2 and 4.4).

Hepatic impairment

The pharmacokinetics of RICOVIR-EM have not been studied in subjects with hepatic impairment.

The pharmacokinetics of emtricitabine have not been studied in non-HBV infected subjects with varying degrees of hepatic insufficiency. In general, emtricitabine pharmacokinetics in HBV infected subjects were similar to those in healthy subjects and in HIV infected patients.

6. Pharmaceutical Particulars

6.1 List of Excipients

Core tablet

Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose

Film coat

FD&C Blue#2
Hypromellose
Lactose monohydrate
Titanium dioxide
Triacetin

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.

6.5 Nature and contents of container

HDPE Bottle of 30 tablets.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Safe disposal instructions about the desiccant: desiccant bag or its contents must not be chewed, swallowed or torn. It should be disposed of intact.

7. Supplier

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8. Date of first Approval

13-June-2016

9. Date of Revision Of The Text

May 2024

References

SmPC of Truvada film-coated tablets - Updated 17-Aug-2023 available at
<https://www.medicines.org.uk/emc/product/3890/smpc/print> | Gilead Sciences Ltd