PROFESSIONAL INFORMATION EMTROC TABLETS

SCHEDULING STATUS

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APPROVED
By Melinda Badenhorst at 8:36 am, Jun 05, 2023

1. NAME OF THE MEDICINE

EMTROC TABLETS (Film-coated tablet)

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 4.4).

EMTROC TABLETS ARE NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF EMTROC TABLETS HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV-1. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRICITABINE (200 mg) OR TENOFOVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE EMTROC TABLETS AND ARE COINFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

EMTROC TABLETS USED FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) INDICATION MUST ONLY BE PRESCRIBED TO INDIVIDUALS CONFIRMED TO BE HIV-NEGATIVE IMMEDIATELY PRIOR TO INITIATING AND PERIODICALLY (AT LEAST ONCE EVERY 3 MONTHS) DURING USE.

RESISTANT HIV-1 VARIANTS HAVE BEEN IDENTIFIED WITH USE OF EMTROC TABLETS FOR A PRE-EXPOSURE PROPHYLAXIS (PrEP) INDICATION FOLLOWING UNDETECTED ACUTE HIV-1 INFECTION. DO NOT INITIATE EMTROC TABLETS FOR A PRE-EXPOSURE PROPHYLAXIS (PrEP) INDICATION IF SIGNS OR SYMPTOMS OF ACUTE HIV-1 INFECTION ARE PRESENT UNLESS NEGATIVE INFECTION STATUS IS CONFIRMED.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

200 mg emtricitabine and 300 mg of tenofovir disoproxil fumarate.

Contains sugar (88,0 mg lactose monohydrate).

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Blue coloured capsule shaped film-coated tablets.

Blue coloured capsule shaped, biconvex, film-coated tablets debossed "L 24" on one side of the tablet and plain on other surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EMTROC TABLETS is indicated in combination with other antiretroviral medicines (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

EMTROC TABLETS is indicated in combination with safer sex practices for Pre-Exposure Prophylaxis (PrEP) in proven HIV-1 uninfected adults to reduce the risk of sexually acquired HIV-1 in adults at high risk, provided maximum treatment compliance can be monitored.

4.2 Posology and method of administration

Posology

Dosage in adults for treatment of HIV-1 infection

The dose of **EMTROC TABLETS** is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Dosage for Pre-Exposure Prophylaxis

The dose of **EMTROC TABLETS** in HIV-1 uninfected adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Special populations

Significantly increased medicine exposures occurred when emtricitabine (200 mg) or tenofovir were administered to subjects with moderate to severe renal impairment (see **4.3**).

Table 1: Dosage for HIV-1 infected patients with creatinine clearance ≥ 50 mL/min

	Creatinine clearance (mL/min)[1]
	≥ 50
Recommended dosing interval	Every 24 hours

[1] Calculated using ideal (lean) body weight

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in all individuals (see **4.3**, 4.4).

Paediatrics: The safety and efficacy of **EMTROC TABLETS** in children under 18 years of age has not been established.

Method of administration:

Once daily taken orally with or without food.

The coated tablets should not be chewed.

4.3 Contraindications:

- **EMTROC TABLETS** is contraindicated in patients with previously demonstrated hypersensitivity to emtricitabine, tenofovir or any of the excipients listed in section 6.1.
- Pregnancy and lactation.
- Creatinine CL < 60 mL/min when used for PrEP.
- Creatinine CL < 50 mL/min when used for treatment of HIV-1.
- **EMTROC TABLETS** should not be co-administered with other tenofovir-containing products, or with other emtricitabine-containing products. **EMTROC TABLETS** should not be administered with lamivudine-containing products due to similarities between emtricitabine and lamivudine.

- **EMTROC TABLETS** should not be used for Pre-Exposure Prophylaxis (PrEP) in individuals with unknown or positive HIV-1 status.
- **EMTROC TABLETS** should not be used for PrEP in individuals not fully committed to full treatment compliance.

4.4 Special warnings and precautions for use

- There are no study results demonstrating the effect of **EMTROC TABLETS** on clinical progression of HIV-1.
- It is not recommended that **EMTROC TABLETS** be used as a triple nucleoside regimen.
- Individuals should be warned that full compliance with treatment is essential to the efficacy in preventing HIV-1 transmission and should be fully informed about the use of other preventative measures including barrier contraception (condoms). Individuals not fully committed or trusted to be treatment-compliant should not use **EMTROC TABLETS** for HIV-1 transmission prophylaxis.

Lactic Acidosis/Hyperlactataemia:

Use of **EMTROC TABLETS** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.

- Lactate 5-10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, 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 **EMTROC TABLETS** to patients with known risk factors for liver disease.

Treatment with **EMTROC TABLETS** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Pancreatitis:

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

Liver disease

Use of **EMTROC TABLETS** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **EMTROC TABLETS** has not been established in patients with significant underlying liver disorders/diseases. 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.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues such as **EMTROC TABLETS** have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above), other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs and symptoms.

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

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines. Patients co-infected with HIV and HBV who discontinue **EMTROC TABLETS** 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.

Renal Impairment:

In patients with moderate to severe renal impairment, the terminal half-life of **EMTROC TABLETS** is increased due to decreased clearance.

EMTROC TABLETS is contraindicated and should not be administered to patients with creatinine clearance below 50 mL/min or patients requiring haemodialysis, or for pre-exposure prophylaxis in patients with creatinine clearance below 60 mL/min (see **4.3**).

If a decrease in creatinine clearance is observed in uninfected individuals while using **EMTROC TABLETS** for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see **4.3**).

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 (see **4.8**). The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic medicines, however, some cases occurred in patients without identified risk factor.

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

Medicine Interactions:

Coadministration of tenofovir disoproxil fumarate and didanosine is not recommended. Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60 % increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse reactions (see **4.5**).

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

Tenofovir decreases the AUC and C_{min} of atazanavir. When coadministered with **EMTROC TABLETS**, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg.

Atazanavir without ritonavir should not be coadministered with EMTROC TABLETS.

Emtricitabine and tenofovir disoproxil fumarate: Since emtricitabine and tenofovir are primarily eliminated by the kidney, coadministration of **EMTROC TABLETS** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentration of emtricitabine, tenofovir and/or other renally eliminated medicines. Some examples include, but are not limited to aciclovir, adefovir dipivoxil, cidofovir, ganciclovir, and valganciclovir.

EMTROC TABLETS is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. **EMTROC TABLETS** should not be coadministered with emtricitabine, or tenofovir. Due to similarities between emtricitabine and lamivudine, **EMTROC TABLETS** should not be coadministered with other medicines containing lamivudine and zidovudine coformulation, lamivudine for HIV, lamivudine for HBV, abacavir sulfate and lamivudine coformulation or abacavir sulfate, lamivudine and zidovudine coformulation.

Opportunistic infections:

Patients receiving **EMTROC TABLETS** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore 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 **EMTROC TABLETS**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Comprehensive management to reduce the risk of acquiring HIV-1:

Use **EMTROC TABLETS** for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because **EMTROC TABLETS** is not always effective in preventing the acquisition of HIV-1.

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea).
- Inform uninfected individuals about and support their efforts in reducing sexual risk behaviour.

Use EMTROC TABLETS to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative.

HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only **EMTROC TABLETS**, because **EMTROC TABLETS** alone does not constitute a complete treatment regime for HIV-1 treatment. Therefore, care should be taken to avoid **EMTROC TABLETS** exposure in HIV-infected individuals (see **4.3**).

- **Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating EMTROC TABLETS for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g. fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g. unprotected sex or condom broken during sex with an HIV-1 infected partner) that may have occurred within the last month.**
- **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 or use an approved test as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

- **While using EMTROC TABLETS for a PrEP indication, HIV-1 screening tests should be repeated at least once every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using an approved test as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.**

Counsel uninfected individuals to strictly adhere to the recommended **EMTROC TABLETS** dosing schedule. The effectiveness of **EMTROC TABLETS** in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable medicine levels in clinical trials.

Bone effects:

EMTROC TABLETS decreases bone mineral density. Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). 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 it 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.

Early virologic failure:

Clinical trials in HIV-1 infected subjects have demonstrated that certain regimes that only contain three nucleoside reverse transcriptase inhibitors (NRTIs) are generally less effective than regimes containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported.

Triple nucleoside regimes should therefore be used with caution. Patients on a therapy utilising a triple nucleoside-only regime should be carefully monitored and considered for treatment modification.

Paediatric Use:

Safety and effectiveness in paediatric patients have not been established.

Use in elderly:

Dose selection for the elderly patients 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 intolerance:

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **EMTROC TABLETS**.

4.5 Interaction with other medicines and other forms of interaction

As **EMTROC TABLETS** contains emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these medicines individually may occur with **EMTROC TABLETS**. The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together *versus* each medicine dosed alone.

In vitro and clinical pharmacokinetic interaction studies have shown the potential for CYP450 mediated interactions involving emtricitabine and tenofovir disoproxil fumarate with other medicines is low.

Concomitant use not recommended:

Due to similarities with emtricitabine, **EMTROC TABLETS** should not be administered concomitantly with other cytidine analogues, such as lamivudine. As a fixed combination, **EMTROC TABLETS** should not be administered concomitantly with other medicines containing any of the components, emtricitabine or tenofovir disoproxil fumarate.

EMTROC TABLETS should not be administered concomitantly with adefovir dipivoxil.

Didanosine: The co-administration of **EMTROC TABLETS** and didanosine is not recommended.

Renally eliminated medicines: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of **EMTROC TABLETS** with medicines 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 medicines.

Use of **EMTROC TABLETS** should be avoided with concurrent or recent use of a nephrotoxic medicine. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2.

Other interactions:

Interactions between the components of **EMTROC TABLETS** and protease inhibitors and nucleoside reverse transcriptase inhibitors, are listed in Table 2 below (increase is indicated as "↑", decrease as "↓ ", no change as "↔"). If available, 90 % confidence intervals are shown in parentheses.

Table 2: Interactions between the individual components of EMTROC TABLETS and other medicines

Medicine by therapeutic areas	**Effects on medicine levels Mean percent change in AUC, C_{max}, C_{min} with 90 % confidence intervals if available (mechanism)**	**Recommendation concerning co-administration with EMTROC TABLETS**
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir/Ritonavir/Tenofovir disoproxil fumarate (300 mg daily/100 mg daily/*300 mg daily) *Tenofovir disoproxil 245 mg is equivalent to 300 mg tenofovir disoproxil fumarate	Atazanavir: AUC: ↓25 % (↓ 42 to ↓3) C_{max} : ↓28 % (↓ 50 to ↑ 5) C_{min} : ↓26 % (↓ 46 to ↑ 10) Tenofovir: AUC: ↑ 37 % C_{max} : ↑ 34 % C_{min} : ↑ 29 %	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.
Atazanavir/Ritonavir/Emtricitabine	Interaction not studied.	

Darunavir/Ritonavir/Tenofovir disoproxil fumarate (300 mg daily/100 mg daily/*300 mg daily)	Darunavir: AUC: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 22 % C_{min}: ↑ 37 %	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.
Darunavir/Ritonavir/Emtricitabine	Interaction not studied.	
Lopinavir/Ritonavir/Tenofovir disoproxil fumarate (400 mg twice daily/100 mg twice daily//*300 mg daily)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32 % (↑ 25 to ↑ 38) C_{max}: ↔ C_{min}: ↑ 51 % (↑ 37 to ↑ 66)	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.
Lopinavir/Ritonavir/Emtricitabine	Interaction not studied.	
NRTIs		
Didanosine/Tenofovir disoproxil fumarate	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60 % increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse reactions. Pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and	Co-administration of **EMTROC TABLETS** and didanosine is not recommended.

	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 fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.	
Didanosine/Emtricitabine	Interaction not studied.	
Lamivudine/Tenofovir disoproxil	Lamivudine: AUC: ↓ 3 % (↓ 8 % to ↑ 15) C_{max}: ↓ 24 % (↓ 44 to ↓ 12) C_{min}: NC Tenofovir: AUC: ↓ 4 % (↓ 15 to ↑ 8) C_{max}: ↑ 102 % (↓ 96 to ↑ 108) C_{min}: NC	Lamivudine and **EMTROC TABLETS** should not be administered concomitantly (see **4.4**).
Efavirenz/Tenofovir disoproxil	Efavirenz: AUC: ↓ 4 % (↓ 7 to ↓ 1) C_{max}: ↓ 4 % (↓ 9 to ↑ 2) C_{min}: NC Tenofovir:	No dose adjustment of efavirenz is required.

	AUC: ↓ 1 % (↓ 8 to ↑ 6) C_{max}: ↑ 7 % (↓ 6 to ↑ 22) C_{min}: NC	
ANTI-INFECTIVES		
Hepatitis B virus (HBV) antiviral medicines		
Adefovir dipivoxil /Tenofovir Disoproxil	Adefovir dipivoxil: AUC: ↓ 11 % (↓ 14 to ↓ 7) C_{max}: ↓ 7 % (↓ 13 to ↓ 0) C_{min}: NC Tenofovir: AUC: ↓ 2 % (↓ 5 to ↑ 0) C_{max}: ↓ 1 % (↓ 7 to ↑ 6) C_{min}: NC	Adefovir dipivoxil and **EMTROC TABLETS** should not be administered concomitantly (see **4.4**).
Hepatitis C virus (HCV) antiviral medicines		
Ledipasvir/Sofosbuvir (90 mg/400 mg daily.) + Atazanavir/Ritonavir (300 mg daily /100 mg daily) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg daily)[1]	Ledipasvir: AUC: ↑ 96 % (↑ 74 to ↑ 121) C_{max}: ↑ 68 % (↑ 54 to ↑ 84) C_{min}: ↑ 118 % (↑ 91 to ↑ 150) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42 % (↑ 34 to ↑ 49) Atazanavir: AUC: ↔ C_{max}: ↔	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

	C_{min}: ↑ 63 % (↑ 45 to ↑ 84) Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 45 % (↑ 27 to ↑ 64) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 47 % (↑ 37 to ↑ 58) C_{min}: ↑ 47 % (↑ 38 to ↑ 57)	been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see **4.4**).
Ledipasvir/Sofosbuvir (90 mg/400 mg daily) + Darunavir/Ritonavir (800 mg daily /100 mg daily) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg daily)[1]	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↓ 27 % (↓ 35 to ↓ 18) C_{max}: ↓ 37 % (↓ 48 to ↓ 25) GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir:	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.

	AUC: ↔ C_{max}: ↔ C_{min}: ↑ 48 % (↑ 34 to ↑ 63) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50 % (↑ 42 to ↑ 59) C_{max}: ↑ 64 % (↑ 54 to ↑ 74) C_{min}: ↑ 59% (↑ 49 to ↑ 70)	The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see **4.4**).
Ledipasvir/Sofosbuvir (90 mg/400 mg daily) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg daily)	Ledipasvir: AUC: ↓ 34 % (↓ 41 to ↓ 25) C_{max}: ↓ 34 % (↓ 41 to ↑ 25) C_{min}: ↓ 34 % (↓ 43 to ↑ 24) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔	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 **4.4**).

	C_{min}: ↔ Tenofovir: AUC: ↑ 98 % (↑ 77 to ↑ 123) C_{max}: ↑ 79 % (↑ 56 to ↑ 104) C_{min}: ↑ 163 % (↑ 137 to ↑ 197)	
Ledipasvir/Sofosbuvir (90 mg/400 mg daily) + Emtricitabine/ Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg daily)	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40 % (↑ 31 to ↑ 50) C_{max}: ↔ C_{min}: ↑ 91 % (↑ 74 to ↑ 110)	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 **4.4**).
Ledipasvir/Sofosbuvir (90 mg/400	Sofosbuvir:	No dose adjustment is required.

mg daily) + Dolutegravir (50 mg daily) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg daily)	AUC: ↔ C_{max}: ↔ GS-331007[2] AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Dolutegravir AUC: ↔ Cmax: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 65 % (↑ 59 to ↑ 71) C_{max}: ↑ 61 % (↑ 51 to ↑ 72) C_{min}: ↑ 115 % (↑ 105 to ↑ 126)	The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see **4.4**).
Sofosbuvir/Velpatasvir (400 mg/100 mg daily) + Atazanavir/ Ritonavir (300 mg daily/100 mg daily) + Emtricitabine/ Tenofovir disoproxil (200 mg/245 mg daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42 % (↑ 37 to ↑ 49)	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions

	Velpatasvir: AUC: ↑ 142% (↑ 123 to ↑ 164) C_{max}: ↑ 55 % (↑ 41 to ↑ 71) C_{min}: ↑ 301 % (↑ 257 to ↑ 350) Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 39 % (↑ 20 to ↑ 61) Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 29 % (↑ 15 to ↑ 44) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 55 % (↑ 43 to ↑ 68) C_{min}: ↑ 39 % (↑ 31 to ↑ 48)	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 **4.4**).
Sofosbuvir/Velpatasvir (400 mg/100 mg daily) + Darunavir/ Ritonavir (800 mg daily /100 mg daily) + Emtricitabine/ Tenofovir disoproxil (200 mg/245 mg daily)	Sofosbuvir: AUC: ↓ 28 % (↓ 34 to ↓ 20) C_{max}: ↓ 38 % (↓ 46 to ↓ 29) GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir:	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

	AUC: ↔ C_{max}: ↓ 24 % (↓ 35 to ↓ 11) C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39 % (↑ 33 to ↑ 44) C_{max}: ↑ 55 % (↑ 45 to ↑ 66) C_{min}: ↑ 52 % (↑ 45 to ↑ 59)	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 **4.4**).
Sofosbuvir/Velpatasvir (400 mg/100 mg daily) + Lopinavir/ Ritonavir (800 mg/200 mg daily) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg daily)	Sofosbuvir: AUC: ↓ 29 % (↓ 36 to ↓ 22) C_{max}: ↓ 41 % (↓ 51 to ↓ 29) GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ 30 % (↓ 41 to ↓ 17)	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

	C_{min}: ↑ 63 % (↑ 43 to ↑ 85) Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 42 % (↑ 27 to ↑ 57) C_{min}: ↔	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 **4.4**).
Sofosbuvir/Velpatasvir (400 mg/100 mg daily) + Raltegravir (400 mg twice daily) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Raltegravir:	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 **4.4**).

	AUC: ↔ C_{max}: ↔ C_{min}: ↓ 21 % (↓ 58 to ↑ 48) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40 % (↑ 34 to ↑ 45) C_{max}: ↑ 46 % (↑ 39 to ↑ 54) C_{min}: ↑ 70 % (↑ 61 to ↑ 79)	
Sofosbuvir/Velpatasvir (400 mg/100 mg daily) + Efavirenz/ Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg daily)	Sofosbuvir: AUC: ↔ C_{max}: ↑ 38 % (↑ 14 to ↑ 67) GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↓ 53 % (↓ 61 to ↓ 43) C_{max}: ↓ 47 % (↓ 57 to ↓ 36) C_{min}: ↓ 57 % (↓ 64 to ↓ 48) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔	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.

	C_{min}: ↔ Tenofovir: AUC: ↑ 81 % (↑ 68 to ↑ 94) C_{max}: ↑ 77 % (↑ 53 to ↑ 104) C_{min}: ↑ 121 % (↑ 100 to ↑ 143)	
Sofosbuvir/Velpatasvir (400 mg/100 mg daily) + Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg daily)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40 % (↑ 34 to ↑ 46) C_{max}: ↑ 44 % (↑ 33 to ↑ 55) C_{min}: ↑ 84 % (↑ 76 to ↑ 92)	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 **4.4**).
Sofosbuvir/Velpatasvir/	Sofosbuvir:	Increased plasma

Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg daily)[3] + Darunavir (800 mg daily) + Ritonavir (100 mg daily) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg daily)	AUC: ↔ C_{max}: ↓ 30 % $C_{min:}$ N/A GS-331007[2]: AUC: ↔ C_{max}:↔ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC: ↑ 143 % C_{max}:↑ 72 % C_{min}: ↑ 300 % Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 34 % Ritonavir: AUC: ↑ 45 % C_{max}: ↑ 60 % C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39 % C_{max}: ↑ 48 %	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 **4.4**).

	C_{min}: ↑ 47 %	
Sofosbuvir (400 mg daily) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg daily)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19 % (↓ 40 to ↑ 10) GS-331007[2]: AUC: ↔ C_{max}: ↓ 23 % (↓ 30 to ↑ 16) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25 % (↑ 8 to ↑ 45) C_{min}: ↔	No dose adjustment is required.
Ribavirin/Tenofovir disoproxil	Ribavirin: AUC: ↑ 26 % (↑ 20 to ↑ 32) C_{max}: ↓ 5 % (↓ 11 to ↑ 1) C_{min}: NC	No dose adjustment of ribavirin is required.
Herpes virus antiviral medicines		
Famciclovir/Emtricitabine	Famciclovir: AUC: ↓ 9 % (↓ 16 to ↓ 1) C_{max}: ↓ 7 % (↓ 22 to ↑ 11) C_{min}: NC	No dose adjustment of famciclovir is required.

	Emtricitabine: AUC: ↓ 7 % (↓ 13 to ↓ 1) C_{max}: ↓ 11 % (↓ 20 to ↑ 1) C_{min}: NC	
Antimycobacterials		
Rifampicin/Tenofovir disoproxil	Tenofovir: AUC: ↓ 12 % (↓ 16 to ↓ 8) C_{max}: ↓ 16 % (↓ 22 to ↓ 10) C_{min}: ↓ 15 % (↓ 12 to ↓ 9)	No dose adjustment is required.
ORAL CONTRACEPTIVES		
Norgestimate/Ethinyl estradiol/Tenofovir disoproxil	Norgestimate: AUC: ↓ 4 % (↓ 32 to ↑ 34) C_{max}: ↓ 5 % (↓ 27 to ↑ 24) C_{min}: NC Ethinyl estradiol: AUC: ↓ 4 % (↓ 9 to ↑ 0) C_{max}: ↓ 6 % (↓ 13 to ↑ 0) C_{min}: ↓ 2 % (↓ 9 to ↑ 6)	No dose adjustment of norgestimate/ethinyl estradiol is required.
IMMUNOSUPPRESSANTS		
Tacrolimus/Tenofovir disoproxil/ Emtricitabine	Tacrolimus: AUC: ↑ 4 % (↓ 3 to ↑ 11) C_{max}: ↑ 3 % (↓ 3 to ↑ 9) C_{min}: NC Emtricitabine: AUC: ↓ 5 % (↓ 9 to ↓ 1) C_{max}: ↓ 11 % (↓ 17 to ↓ 5) C_{min}: NC Tenofovir:	No dose adjustment of tacrolimus is required.

	AUC: ↑ 6 % (↓ 1 to ↑ 13) C_{max}: ↑13 % (↑ 1 to ↑ 27) C_{min}: NC	
NARCOTIC ANALGESICS		
Methadone/Tenofovir disoproxil	Methadone: AUC: ↑ 5 % (↓ 2 to ↑ 13) C_{max}: ↑ 5 % (↓ 3 to ↑ 14) C_{min}: NC	No dose adjustment of methadone is required.

NC = not calculated

[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.

Studies conducted with other medicines:

Emtricitabine: In vitro, emtricitabine did not inhibit metabolism mediated by any of the following human CYP450 isoforms: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation.

There are no clinically significant pharmacokinetic interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine or famciclovir.

Tenofovir disoproxil fumarate: Co-administration of lamivudine, indinavir, efavirenz, nelfinavir or saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, adefovir dipivoxil or the hormonal contraceptive norgestimate/ethinyl estradiol with tenofovir disoproxil fumarate did not result in any clinically significant pharmacokinetic interaction.

Atazanavir and lopinavir/ritonavir has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown.

Co-administration of tenofovir disoproxil fumarate and ledipasvir/sofosbuvir or sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase tenofovir exposure. Patients

receiving a regimen containing tenofovir disoproxil fumarate concomitantly with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir should be monitored for adverse reactions associated with tenofovir disoproxil fumarate.

4.6 Fertility, pregnancy and lactation

Safety and use in pregnancy and lactation has not been established (see 4.3).

Pregnancy

There are no adequate and well controlled studies in pregnant women. **EMTROC TABLETS** should not be used in pregnancy.

Breastfeeding

It is not known whether **EMTROC TABLETS** is excreted in human milk.

Breastfeeding Mothers: HIV-1 infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV-1.

Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in breastfed infants, mothers should be instructed not to breastfeed if they are receiving **EMTROC TABLETS**.

4.7 Effects on ability to drive and use machines

EMTROC TABLETS may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

EMTROC TABLETS can have side effects.

Table 3 Tabulated summary of adverse reactions associated with the individual components of EMTROC TABLETS

Frequency	**Emtricitabine**	**Tenofovir disoproxil fumarate**
Blood and lymphatic system disorders:		
Frequency not known	Neutropenia, anaemia, haematuria	Neutropenia, haematuria

Immune system disorders:		
Frequency not known	Angioedema	Allergy, allergic reaction
Metabolism and nutrition disorders:		
Frequent		Hypophosphataemia
Frequency not known	Lactic acidosis, usually associated with severe hepatomegaly and steatosis, hypertriglyceridaemia, hyperglycaemia.	Lactic acidosis, usually associated with severe hepatomegaly and steatosis, hypertriglyceridaemia, hyperglycaemia
Psychiatric disorders:		
Frequency not known	Sleep disturbances (abnormal dreams, insomnia), depressive disorder and anxiety	Depression, anxiety
Nervous system disorders:		
Frequent	Headache	
Frequency not known	Asthenia, dizziness, neuropathy, peripheral neuritis, paraesthesia	Headache, asthenia, dizziness, peripheral neuropathy (including peripheral neuritis, neuropathy).
Respiratory, thoracic and mediastinal disorders:		
Frequency not known	Increased cough and rhinitis, chest pain, pneumonia	Chest pain, pneumonia, dyspnoea
Gastrointestinal disorders:		
Frequent	Nausea, vomiting, diarrhoea	Nausea, vomiting, diarrhoea, abdominal pain, flatulence, dyspepsia and anorexia
Less frequent		Raised serum amylase concentration, pancreatitis
Frequency not known	Abdominal pain, dyspepsia, pancreatitis	Abdominal pain, dyspepsia

Hepatobiliary disorders:		
Frequency not known	Raised liver enzyme concentrations and hyperbilirubinaemia	Raised liver enzymes and hepatitis
Skin and subcutaneous tissue disorders:		
Frequent	Rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).	
Frequency not known	Skin discolouration, manifested by hyperpigmentation on the palm and/or soles.	Skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash).
Musculoskeletal, connective tissue and bone disorders:		
Frequency not known	Arthralgia, myalgia	Back pain, arthralgia, myalgia, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy
Renal and urinary disorders:		
Frequent	Elevation of creatinine kinase	
Frequency not known		Increased creatinine levels, nephritis, nephrogenic diabetes insipidus, renal impairment, acute renal failure, and effects on the renal proximal tubules including Fanconi syndrome, renal failure, proximal

		tubulopathy, proteinuria, acute tubular necrosis
General disorders and administrative site conditions:		
Frequency not known	Fever, sweating, weight loss	Fever, sweating, weight loss

4.9 Overdose

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

Emtricitabine:

Haemodialysis treatment removes approximately 30 % of the emtricitabine dose over a 3-hour dialysis period starting within 1,5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir disoproxil fumarate:

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A20.2.8 Antimicrobial (Chemotherapeutic) agents, Antiviral agents.

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

***Emtricitabine*:** Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI). Emtricitabine, a synthetic nucleoside analogue of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

***Tenofovir disoproxil fumarate*:** Tenofovir disoproxil fumarate is a nucleoside reverse transcriptase inhibitor (NRTI). Tenofovir disoproxil fumarate, also known as tenofovir DF, 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 RT 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.

Antiviral Activity

***Emtricitabine and tenofovir disoproxil fumarate*:** In combination studies evaluating the *in vitro* antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

Resistance

***Emtricitabine and tenofovir disoproxil fumarate*:** HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184I/V and/or K65R amino acid substitutions in the viral RT.

Cross Resistance

***Emtricitabine and tenofovir disoproxil fumarate*:** Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognised. The M184V/I and/or K65R substitutions selected *in vitro* by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours either or both of these amino acid substitutions.

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults

***Emtricitabine*:** The pharmacokinetic properties of emtricitabine are summarised in Table 4.

Absorption: Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 – 2 hours post-dose.

Distribution: *In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 – 200 µg/mL.

Metabolism and elimination: Following administration of radiolabelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine (200 mg), the plasma emtricitabine half-life is approximately 10 hours.

***Tenofovir Disoproxil Fumarate*:** The pharmacokinetic properties of tenofovir disoproxil fumarate are summarised in Table 4.

Absorption: Following oral administration of tenofovir, maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hour.

Distribution: *In vitro* binding of tenofovir to human plasma proteins < 0,7 % and is independent of concentration over the range of 0,01 – 25 µg/mL.

Metabolism and elimination: Approximately 70 – 80 % of the intravenous dose of tenofovir is recovered as unchanged in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 4: Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults[1]

	Emtricitabine	**Tenofovir**
Fasted Oral Bioavailability[2] (%)	92 (83,1 – 106,4)	25 (NC – 45,0)
Plasma Terminal Elimination Half-Life[2] (hr)	10 (7,4 – 18,0)	17 (12,0 – 25,7)
C_{max}[3] (µg/mL)	1,8 ± 0,72[4]	0,30 ± 0,09
AUC[3] (µg•hr/mL)	10,0 ± 3,12[4]	2,29 ± 0,69
CL/F[3](mL/min)	302 ± 94	1043 ± 115
CL_{renal}[3] (mL/min)	213 ± 89	243 ± 33

[1] NC = Not calculated

[2]Median (range)

[3] Mean (± SD)

[4] Data presented as steady state values.

Effects of Food on Oral Absorption

EMTROC TABLETS may be administered with or without food. Administration of **EMTROC TABLETS** following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delays the time of tenofovir C_{max} by approximately 0,75 hour. The mean increases in tenofovir AUC and C_{max} are approximately 35 % and 15 %, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. Emtricitabine systemic exposures (AUC and C_{max}) are unaffected when **EMTROC TABLETS** is administered with either a high fat or a light meal.

Special Populations

Paediatric and Elderly Patients

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in children (< 18 years) or in elderly (> 65 years) (see **4.4**).

Patients with Impaired Renal Function

The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment (See **4.4).** In patients with creatinine clearance < 50 mL/min, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased. **EMTROC TABLETS** should not be used in patients with creatinine clearance < 50 mL/min and in patients with end-stage renal disease requiring dialysis (see **4.4**).

Do not use **EMTROC TABLETS** for a Pre-exposure Prophylaxis (PrEP) indication in HIV-1 uninfected individuals with a creatinine clearance < 60 ml/min (see **4.3**).

Patients with Hepatic Impairment:

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. The pharmacokinetics of **EMTROC TABLETS** or emtricitabine have not

been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolised by liver enzymes, so the impact of liver impairment should be limited.

5.3 Preclinical safety data

Emtricitabine: Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

Tenofovir disoproxil: Non-clinical safety pharmacology studies on tenofovir disoproxil reveal no special hazard for humans. 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 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 toxicity 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 a periand postnatal toxicity study at maternally toxic doses.

Combination of emtricitabine and tenofovir disoproxil: Genotoxicity and repeated dose toxicity studies of one month or less with the combination of these two components found no exacerbation of toxicological effects compared to studies with the separate components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pre-gelatinized starch, coating containing hydroxypropylmethylcellulose, lactose monohydrate, titanium dioxide (Colour Index No. 77891), triacetin, FD&C Blue No.2 (Colour Index No. 73015).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the manufacturing date in HDPE container pack.

24 months from the manufacturing date in Alu-Alu blister pack.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep the containers tightly closed.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

1. HDPE Container. Pack of 28 or 30 tablets.

75 ml white, heavy weight, round white HDPE bottle with 38-400 neck finish with a 38 mm white child resistant closure with pulp and heat seal liner containing a 3 g silica gel sachet.

2. Alu-Alu blister pack (10 X 10) tablets

Cold form laminate 25 micron OPA/45 micron Aluminium foil/60 micron PVC and plain 25 micron aluminium foil with 6-8 GSM HSL.

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

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)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

Revision date: To be advised