Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DUOTEMTRIC Film-coated Tablets

WARNINGS:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE SECTION 4.4).

DUOTEMTRIC IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF DUOTEMTRIC HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED DUOTEMTRIC.

HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS INFECTED WITH HBV WHO DISCONTINUE THE COMBINATION TABLET. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE SECTION 4.4).

DUOTEMTRIC 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 EMTRICITABINE + TENOFOVIR DF FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) INDICATION FOLLOWING UNDETECTED ACUTE HIV-1 INFECTION. DO NOT INITIATE DUOTEMTRIC FOR A PRE-EXPOSURE PROPHYLAXIS (PrEP) INDICATION IF SIGNS OR SYMPTOMS OF ACUTE HIV-1

INFECTION ARE PRESENT UNLESS NEGATIVE INFECTION STATUS IS CONFIRMED (SEE SECTION 4.4).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate (which is equivalent to 245 mg tenofovir disoproxil).

Contains sugar: lactose 50 mg per tablet.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated Tablets:

White to off white, capsule shaped, film coated tablets debossed with 'RF14' on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **DUOTEMTRIC** 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.
- **DUOTEMTRIC** 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 infection 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 **DUOTEMTRIC** 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 **DUOTEMTRIC** 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.

If a dose of **DUOMETRIC** is missed within 12 hours of the time it is usually taken, **DUOTEMTRIC** should be taken as soon as possible and the normal dosing schedule should be resumed. If a dose of **DUOTEMTRIC** is missed by more than 12 hours and it is almost time for the next dose, the missed dose should not be taken and the usual dosing schedule should be resumed.

If vomiting occurs within an hour of taking **DUOTEMTRIC**, another tablet should be taken.

If vomiting occurs more than 1 hour after taking **DUOTEMTRIC** a second dose should not be taken.

Renal impairment:

Significantly increased medicine exposures occurred when emtricitabine or tenofovir disoproxil fumarate were administered to patients with moderate to severe renal impairment (see Section 4.3).

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

	Creatinine Clearance (mL/min)*
	≥ 50
Recommended Dosing Interval	Every 24 hours

* Calculated using ideal (lean) body weight

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

Method of administration

Oral use.

DUOTEMTRIC may be taken with or without food.

4.3 Contraindications

- **DUOTEMTRIC** is contra-indicated in patients with previously demonstrated hypersensitivity to emtricitabine, tenofovir disoproxil fumarate, or to any of the other components of **DUOTEMTRIC**.
- Creatinine CL < 60 ml/min when used for PrEP.
- Creatinine CL < 50 ml/min when used for treatment of HIV-1.

- Pregnancy and lactation (see Section 4.6).
- **DUOTEMTRIC** should not be co-administered with other tenofovir-containing products, or with other emtricitabine-containing products. **DUOTEMTRIC** should not be administered with lamivudine-containing products due to the similarities between emtricitabine and lamivudine.
- **DUOTEMTRIC** should not be used for PrEP in individuals with unknown or positive HIV-1 status.
- **DUOTEMTRIC** 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 reported study results demonstrating the effect of **DUOTEMTRIC** on clinical progression of HIV-1.
- It is not recommended that **DUOTEMTRIC** be used as a component of 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 **DUOTEMTRIC** for HIV-1 transmission prophylaxis.

Lactic Acidosis / hyperlactataemia

Use of **DUOTEMTRIC** 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 responds as follows:

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

- Lactate 5 – 10 mmol/l: with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate > 10 mmol/l:: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering **DUOTEMTRIC** to patients with known risk factors for liver disease.

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

Mitochondrial dysfunction

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

Pancreatitis

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

Liver Disease

Use of **DUOTEMTRIC** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **DUOTEMTRIC** has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C. please also consult the relevant package insert for these medicines.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

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

Patients with chronic hepatitis B or C and treated with antiretroviral therapy such as **DUOTEMTRIC** are at an increased risk for severe and potentially fatal hepatic adverse reactions. Patients co-infected with HIV and HBV who discontinue **DUOTEMTRIC** should be closely monitored with both clinical and laboratory follow-up after stopping treatment. 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). **DUOTEMTRIC** is not indicated for the treatment of HBV infection and the safety and efficacy of **DUOTEMTRIC** has not been established in patients co-infected with HBV and HIV.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package insert for these medicines. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Discontinuation of **DUOTEMTRIC** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis which may lead to hepatic decompensation and liver failure.

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating **DUOTEMTRIC** therapy. Hepatic function should be closely monitored with both

clinical and laboratory follow-up for at least several months in patients who discontinue **DUOTEMTRIC** and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir disoproxil fumarate (see Section 4.3).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during treatment with **DUOTEMTRIC**. Routine monitoring of calculated creatinine clearance and serum phosphorous should be performed in patients at risk for renal impairment (see Section 4.3).

DUOTEMTRIC should be avoided with concurrent or recent use of a nephrotoxic agent.

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.

DUOTEMTRIC 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 Section 4.3).

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

Renal management in Pre-exposure Prophylaxis

DUOTEMTRIC for a PrEP indication is not recommended for use in population if estimated creatinine clearance is less than < 60 ml/min. 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 **DUOTEMTRIC** for pre-exposure prophylaxis, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations.

Consideration should be given to interrupting use of with **DUOTEMTRIC** in individuals with creatinine clearance decreased to < 60 ml/min or decrease in serum phosphate to <1,0 gm/dL (0,32mmol/L). Interrupting use of **DUOTEMTRIC** should also be considered in case of progressive decline of renal function when no other cause has been identified.

Interactions

DUOTEMTRIC is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. **DUOTEMTRIC** should not be co-administered with other medicines containing emtricitabine or tenofovir (see Section 4.3).

Due to similarities between emtricitabine and lamivudine, **DUOTEMTRIC** should not be co-administered with other medicines containing lamivudine, including lamivudine and zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulphate and lamivudine co-formulation or abacavir sulphate, lamivudine and zidovudine co-formulation (see Section 4.3).

Co-administration of didanosine buffered tablet formulation with **DUOTEMTRIC** should be under fasted conditions (see Section 4.5).

Co-administration of **DUOTEMTRIC** and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events (see Section 4.8).

Patients receiving atazanavir and lopinavir/ritonavir and **DUOTEMTRIC** should be monitored for **DUOTEMTRIC**-associated adverse events. **DUOTEMTRIC** should be discontinued in patients who develop **DUOTEMTRIC**-associated adverse events (see Section 4.8).

Tenofovir decreases the AUC and C_{min} of atazanavir (see Section 4.5). When co-administered with **DUOTEMTRIC**, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be co-administered with **DUOTEMTRIC**.

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of **DUOTEMTRIC** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated medicines (see Section 4.5). Some examples include, but are not limited to adefovir dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.

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 **DUOTEMTRIC** is co-administered with an NSAID, renal function should be monitored adequately.

Osteonecrosis

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.

Bone mineral density

During therapy with **DUOTEMTRIC** assessment of bone mineral density (BMD) should be considered for patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. The effect of supplementation with calcium and vitamin D has not been studied. If bone abnormalities are suspected then appropriate consultation should be obtained.

Bone mineral density monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia.

Tenofovir combination therapy is associated with decreased bone mineral density.

Cases of osteomalacia (associated with proximal renal tubulopathy have been reported in association with the use of tenofovir DF, such as **DUOTEMTRIC** (see Section 4.8).

Lipodystrophy and metabolic abnormalities

Redistribution/accumulation of body fat including central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy.

The mechanism and long term consequences of these events are currently unknown. A causal relationship has not been established.

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 pathogenic-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are pulmonary tuberculosis, cytomegalovirus retinitis, Pneumocystis jirovecii pneumonia (PCP), cryptococcal meningitis, and other forms of tuberculosis and atypical myco-bacterial infections. Appropriate treatment of the opportunistic diseases 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 Grave's 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.

Paediatrics

Safety and efficacy in paediatric patients have not been established

Geriatrics

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 disease or other medicine therapy.

Opportunistic Infections

Patients receiving **DUOTEMTRIC** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by medical practitioners 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 **DUOTEMTRIC** has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precaution should continue to be employed.

Comprehensive management to reduce the risk of acquiring HIV-1

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

- Counsel uninfective 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 gonorrhoea).
- Inform uninfected individuals about and support their efforts in reducing sexual risk behaviour.

Use **DUOTEMTRIC** 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 **DUOTEMTRIC**, because **DUOTEMTRIC** alone does not constitute a complete treatment regime for HIV-1 treatment. Therefore, care should be taken to avoid **DUOTEMTRIC** exposure in HIV-infected individuals (see Section 4.3).

- Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage or infection. Prior to initiating **DUOTEMTRIC** 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) exposure 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 **DUOTEMTRIC** for a PrEP indication, HIV-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.

Council uninfected individuals to strictly adhere to the recommended **DUOTEMTRIC** dosing schedule. The effectiveness of **DUOTEMTRIC** in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measureable dug levels in clinical trials.

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.

Lactose warning

DUOTEMTRIC tablets contain lactose as an excipient. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **DUOTEMTRIC**.

4.5 Interaction with other medicinal products and other forms of interaction

No medicine interaction studies have been conducted using **DOUTEMTRIC** tablets.

DUOTEMTRIC: The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when administered together versus each agent alone.

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

DOUTEMTRIC is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No interactions due to competition for renal excretion have been reported; however, co-administration of **DOUTEMTRIC** with medicines that are eliminated by active tubular secretion may

increase concentrations of emtricitabine by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the co-administered medicine.

Medicines that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

No clinical significant interactions have been observed between emtricitabine and famiciclovir, indinavir, zidovudine, stavudine, and tenofovir disoproxil fumarate (see Tables 1 and 2). Similarly, no clinically significant interactions have been observed between tenofovir disoproxil fumarate and abacavir, adefovir dipivoxil, ribavirin, efafirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, and saquinavir/ritonavir in studies conducted in healthy volunteers (see Tables 3 and 4).

Table 2

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

Co-administered medicine	**Dose of co-administered medicine (mg)**	**Emtricitabine Dose (mg)**	**N**	**% Change of emtricitabine pharmacokinetic parameters[2] (90 % CI)**		
				C_{max}	**AUC**	**C_{min}**
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	↔	↔	↑20 (↑12 to ↑29)
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↔	↔	↔
Indinavir	800 x 1	200 x 1	12	↔	↔	NA
Famciclovir	500 x 1	200 x 1	12	↔	↔	NA
Stavudine	40 x 1	200 x 1	6	↔	↔	NA

1. **All interaction studies conducted in healthy volunteers.**
2. **↑ = Increase; ↓ = Decrease; ↔ = No Effect; NA = Not Applicable.**

Table 3

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

Co-administered medicine	Dose of co-administered medicine (mg)	Emtricitabine Dose (mg)	N	% Change of co-administered medicine pharmacokinetic parameters[2] (90 % CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	↔	↔	↔
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↑17 (↑0 to ↑38)	↑13 (↑5 to ↑20)	↔
Indinavir	800 x 1	200 x 1	12	↔	↔	NA
Famciclovir	500 x 1	200 x 1	12	↔	↔	NA
Stavudine	40 x 1	200 x 1	6	↔	↔	NA

1. **All interaction studies conducted in healthy volunteers.**
2. **↑ = Increase; ↓ = Decrease; ↔ = No Effect; NA = Not Applicable.**

Table 4

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

Co-administered medicine	Dose of co-administered medicine (mg)	N	% Change of tenofovir pharmacokinetic parameters[2] (90 % CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↔	↔	NC
Adefovir dipivoxil	10 once	22	↔	↔	NC
Atazanavir[3]	400 once daily x 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Didanosine (enteric coated)	400 once	25	↔	↔	↔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	↔	↔	↔
Efavirenz	600 once daily x 14 days	29	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↔
Indinavir	800 three times daily x 7 days	13	↑14 (↓8 to ↑33)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↔	↔	↔

Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	↔	↑32 (↑25 to ↑38)	↑51 (↑37 to ↑66)
Nelfinavir	1 250 twice daily x 14 days	29	↔	↔	↔
Saquinavir/ Ritonavir	1 000/100 twice daily x 14 days	35	↔	↔	↑23 (↑16 to ↑30)

1. **Patients received tenofovir DF 300 mg once daily.**
2. **↑ = Increase; ↓ = Decrease; ↔ = No Effect; NC = Not Calculated.**
3. **Reyataz South African Prescribing Information (Bristol-Myers Squibb).**

Table 5

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

Co-administered medicine	**Dose of co-administered medicine (mg)**	**N**	**% Change of co-administered medicine pharmacokinetic parameters[1] (90 % CI)**		
			C_{max}	**AUC**	**C_{min}**
Abacavir	300 once	8	↑12 (↓1 to ↑26)	↔	NA
Adefovir dipivoxil	10 once	22	↔	↔	NA
Atazanavir[2]	400 once daily x 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir[2]	400/ Ritonavir 300/100 once daily for 42 days	10	↓28 (↓50 to ↓5)	↓25[3] (↓42 to ↓3)	↓23[3] (↓46 to ↓10)
Efavirenz	600 once daily x 14 days	30	↔	↔	↔
Emtricitabine	200 once daily x 7 days	17	↔	↔	↑20 (↑12 to ↑29)
Indinavir	800 three times daily x 7 days	12	↓11 (↓30 to ↑12)	↔	↔
Lamivudine	150 twice daily x 7 days	15	↓24 (↓34 to ↓12)	↔	↔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	↔	↔	↔
Methadone[4]	40 to 110 once daily x 14 days[5]	13	↔	↔	↔
Nelfinavir M8 metabolite	1 250 twice daily x 14 days	29	↔	↔	↔
Oral Contraceptives[6]	Ethinyl Estradiol 0,035 mg/ Norgestimate 0,25 mg once daily x 7 days	20	↔	↔	↔
Ribavirin	600 once	22	↔	↔	NA
Saquinavir Ritonavir	Saquinavir/ Ritonavir 1 000/100 twice daily x 14 days	32	↑22 (↑6 to ↑41)	↑29[7] (↑12 to ↑48)	↑47[7] (↑23 to ↑76) ↑23 (↑3 to ↑46)

			↔	↔	

1. **↑ = Increase; ↓ = Decrease; ↔ = No Effect; NC = Not Calculated.**
2. **Reyataz South African Prescribing Information (Bristol-Myers Squibb).**
3. **In HIV infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2,3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.**
4. **R-(active), S-and total methadone exposure were equivalent when dosed alone or with tenofovir DF.**
5. **Individual subjects were maintained on their stable methadone dose. No pharmacodynamics alterations (opiate toxicity or withdrawal signs or symptoms) were reported.**
6. **Ethinyl estradiol 0,035 mg and 17-deacetyl norgestimate 0,25 mg (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir DF.**
7. **Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are co-administered.**

Table 6

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

Didanosine[1] dose (mg)/ Method of administration[2]	**Tenofovir method of administration[2]**	**N**	**% Difference (90 % CI) vs. didanosine 400 mg alone, fasted[3]**	
			C_{max}	**AUC**
Buffered tablets				
400 once daily[4] x 7 days	Fasted 1 hour after didanosine	14	↑28 (↑11 to ↑48)	↑44 (↑31 to ↑59)
Enteric-coated tablets				
400 once, fasted	With food 2 hours after didanosine	26	↑48 (↑25 to ↑76)	↑48 (↑31 to ↑67)
400 once, with food	Simultaneously with didanosine	26	↑64 (↑41 to ↑89)	↑60 (↑44 to ↑79)
250 once, fasted	With food, 2 hours after didanosine	28	↓10 (↓22 to ↑3)	↔
250 once, fasted	Simultaneously with didanosine	28	↔	↑14 (0 to ↑31)
250 once, with food	Simultaneously with didanosine	28	↓29 (↓39 to ↓18)	↓11 (↓23 to ↑2)

1. **See WARNINGS AND SPECIAL PRECAUTIONS regarding use of didanosine with tenofovir.**
2. **Administration with food was with a light meal (~373 kcal % fat).**
3. **↑ = Increase; ↓ = Decrease; ↔ = No Difference.**
4. **Includes 4 subjects weighing < 60 kg receiving ddI 250 mg.**

4.6 Fertility, pregnancy and lactation

The safety of **DUOTEMTRIC** in pregnancy and lactation has not been established (see Section 4.3).

A reliable method of contraception should be used to avoid pregnancy while taking **DUOTEMTRIC**.

Pregnancy

DUOTEMTRIC should not be used during pregnancy (see Section 4.3).

Breast-feeding

HIV infected mothers should not breast-feed their infants, to avoid risking post-transmission of HIV.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in breast-fed infants, mothers should be instructed not to breast-feed if they are receiving

DUOTEMTRIC.

Fertility

No data available

4.7 Effects on ability to drive and use machines

DUOTEMTRIC tablets have the ability to cause asthenia and dizziness, so care should be taken whilst driving or operating machinery.

4.8 Undesirable effects

Table 7 Tabulated list of adverse events observed and reported during treatment with Emtricitabine and Tenofovir disoproxil fumarate

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and lymphatic system disorders	Frequent	Neutropenia
	Frequency unknown	Anaemia
Immune system disorders	Frequent	Allergic reaction, including angioedema
Metabolism and nutrition disorders	Frequent	Hypertriglyceridemia, hyperglycaemia
	Frequency unknown	Hypophosphataemia, lactic acidosis, hypokalaemia
Psychiatric disorders	Frequent	Insomnia, abnormal dreams
Nervous system disorders	Frequent	Dizziness, headache
Respiratory, thoracic, and mediastinal disorders	Frequent	Dyspnoea
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting, flatulence, dyspepsia, abdominal pain, amylase elevation, lipase elevation

Hepatobiliary disorders	Frequent	Hyperbilirubinaemia, increased liver enzymes (including increased AST, increased ALT and/or gamma GT).
	Frequency unknown	Hepatitis, hepatic steatosis
Skin and subcutaneous tissue disorders	Frequent	Rash event (rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash), skin discolouration
Muscoskeletal and connective tissue disorders	Frequent	Creatinine kinase elevation
	Frequency unknown	Myopathy, osteomalacia (both associated with proximal renal tubulopathy), rhapdomyolysis, muscular weakness
Renal and urinary disorders	Frequency unknown	Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases)
General disorders and administration site conditions	Frequent	Pain, asthenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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 poorly removed by haemodialysis. Following a single 300 mg dose of tenofovir, a four-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.20.2.8. Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents. Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR03.

Pharmacodynamic properties

Emtricitabine*:* 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'-triphospate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumerate: Tenofovir disoproxil fumerate 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 disphosphate.

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 polymerase 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 reported.

Resistance:

Emtricitabine and Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in vitro. Genotypic analysis of these isolates identified the M1841/V and/or K65R amino acid substitutions in the viral RT.

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected in cell culture and *in vivo.* Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir disoproxil fumarate**:** HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in RT and showed a 2 – 4 fold reduction in susceptibility to tenofovir.

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 reported 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.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility *in vitro* to didanosine, stavudine, tenofovir, zidovudine and the NNRTIs (delavirdine, efavirenz and nevirapine). Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitution may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir, didanosine, tenofovir and zalcitabine, demonstrated reduced

susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir disoproxil fumarate: HIV-1 isolates from patients whose HIV-1 expressed a mean of 3' zidovudine associated RT amino acid substitutions (M41L, D67N, K7OR, L210W, T215Y/F or K219Q/E/N) showed a 3,1 fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of emtricitabine and tenofovir disoproxil fumarate are summarised in Table 8.

Table 8

Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir disoproxil fumarate

	Emtricitabine	**Tenofovir DF**
Fasted Oral Bioavailability[2] (%)	92 (83,1 to 106,4)	25 (NC[1] to 45,0)
Plasma Terminal Elimination Half-Life[2] (hour)	10 (7,4 to 18,0)	17 (12,0 to 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] Not calculated

[2] Median (range)

[3] Mean (± SD)

[4] Data presented as steady state values

Absorption

Emtricitabine: Emtricitabine is rapidly absorbed after oral administration with peak plasma concentrations occurring at 1–2 hours post-dose.

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

Effects of Food on Oral Absorption:

The combination tablet may be administered with or without food. Administration of the combination tablet following a high fat mean (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0,75 hour. The mean increases in tenofovir AUC and C_{max} were 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}) were unaffected when the combination tablet was administered with either a high fat or a light meal.

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.

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

Biotransformation

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.

Approximately 70 to 80 % of the intravenous dose of tenofovir is recovered as unchanged drug in the urine.

Elimination

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 is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir, the terminal elimination half-life is approximately 17 hours.

Special Populations:

Race

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of emtricitabine (200 mg).

Tenofovir disoproxil fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of tenofovir disoproxil fumarate.

Paediatric and Geriatric Patients

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in children (<12 years weighing less than 35 kg) or in the elderly (> 65 years) (see Section 4.4).

Patients with Impaired Renal Function

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment (see Sections 4.3 and 4.4**).** In patients with creatinine clearance < 50 ml/min, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were significantly increased. It is recommended that **DUOTEMTRIC** not be used in patients with creatinine clearance < 50 ml/min or in patients with end-stage renal disease requiring dialysis (see Sections 4.3 and 4.4).

Do not use **DUOTEMTRIC** for a Pre-exposure Prophylaxis (PrEP) indication in HIV-1 uninfected individuals with a creatinine clearance < 60 ml/min (see Sections 4.3 and 4.4).

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been reported in non-HIV infected patients with moderate to severe hepatic impairment. There were

no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of the combination tablet or emtricitabine has not been studied in patients 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

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, anhydrous lactose, pregelatinised starch, magnesium stearate, croscarmellose sodium, Opadry II 31K58902 white (which consists of lactose monohydrate, hypromellose, titanium dioxide, triacetin).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C, protected from moisture.

KEEP WELL CLOSED.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Primary Pack

The product is packed in a white opaque, round cylindrical HDPE bottle with CRC /Screw cap.

The bottle is a white, opaque 100 cc /200 cc HDPE bottle with white polypropylene, round cylindrical 38 mm CRC/Screw cap with heat seal liner.

The bottle pack contains 30 and 90 tablets.

The bottle also contains desiccant sachet.

Secondary Pack

HDPE bottle pack can be supplied with or without a carton.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road, Stomill, Ext 1

Roodepoort, 1724

8. MARKETING AUTHORISATION NUMBER(S)

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