SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

MYTENOTRIN film-coated tablets

Tenofovir disoproxil fumarate 300 mg and Emtricitabine 200 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Tenofovir disoproxil fumarate	300 mg
Emtricitabine	200 mg
Contains: Sugar (lactose monohydrate)	136 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MYTENOTRIN 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.

MYTENOTRIN 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

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

Dosage in adults for treatment of HIV-1 infection

The dose of MYTENOTRIN 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 MYTENOTRIN 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.

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)

	Creatine 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 Section 4.3, 4.4 and Renal impairment).

Method of administration

Oral administration. It is preferable that MYTENOTRIN is taken with food.

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

4.3 Contraindications

MYTENOTRIN is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of MYTENOTRIN.

- Pregnancy and lactation.
- Creatinine CL < 60 mL/min when used for PrEP.
- Creatinine CL < 50 mL/min when used for treatment of HIV-1.

- MYTENOTRIN should not be co-administered with other tenofovir-containing medicines, or with other emtricitabine-containing medicines. MYTENOTRIN should not be administered with lamivudine-containing medicines due to similarities between emtricitabine and lamivudine.
- MYTENOTRIN should not be used for Pre-Exposure Prophylaxis (PrEP) in individuals with unknown or positive HIV-1 status.
- MYTENOTRIN should not be used for PrEP in individuals not fully committed to full treatment compliance.

4.4 Special warnings and precautions for use

WARNINGS:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS. MYTENOTRIN IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF MYTENOTRIN 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 MYTENOTRIN.

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 MYTENOTRIN AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED.

MYTENOTRIN USED FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) 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 MYTENOTRIN FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) FOLLOWING UNDETECTED ACUTE HIV-1 INFECTION. DO NOT INITIATE MYTENOTRIN FOR THE PRE-EXPOSURE PROPHYLAXIS (PrEP) INDICATION IF SIGNS OR SYMPTOMS OF ACUTE HIV-1 INFECTION ARE PRESENT, UNLESS NEGATIVE INFECTION STATUS IS CONFIRMED.

- There are no study results demonstrating the effect of MYTENOTRIN on clinical progression of HIV-1.
- It is not recommended that MYTENOTRIN 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 MYTENOTRIN for HIV-1 transmission prophylaxis.

Patients with HIV-1 harbouring mutations:

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

Lactic acidosis/severe hepatomegaly with steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues such as MYTENOTRIN alone or in combination with other antiretrovirals. This is caused by mitochondrial dysfunction. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues such as MYTENOTRIN to any patient with known risk factors for liver disease, however, cases have also been reported in patients with no known risk factors. Treatment with MYTENOTRIN should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2 to 5 mmol/L with minimum symptoms: Switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5 to 10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop MYTENOTRIN 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 MYTENOTRIN to patients with known risk factors for liver disease.

Treatment with MYTENOTRIN 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 MYTENOTRIN. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of MYTENOTRIN until diagnosis of pancreatitis is excluded.

Liver disease:

Use of MYTENOTRIN can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of MYTENOTRIN 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 MYTENOTRIN 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 such as MYTENOTRIN, are at an increased risk for severe and potentially fatal hepatic adverse reactions. Patients co-infected with

HBV to discontinue MYTENOTRIN, 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). MYTENOTRIN is not indicated for the treatment of chronic HBV infection and the safety and efficacy of MYTENOTRIN have 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 inserts 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 MYTENOTRIN therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis which may lead to liver decompensation and liver failure.

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating MYTENOTRIN therapy. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are co-infected with HIV and HBV and discontinue MYTENOTRIN. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal impairment:

MYTENOTRIN is 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 therapy with MYTENOTRIN. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment (see section 4.3).

MYTENOTRIN should be avoided with concurrent or recent use of a nephrotoxic medicine. MYTENOTRIN 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 creatinine clearance is observed in uninfected individuals while using MYTENOTRIN for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use (see section 4.3).

Co-administration of other medicines:

MYTENOTRIN is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate.

MYTENOTRIN should not be co-administered with other medicines containing emtricitabine or tenofovir (see section 4.3).

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

Co-administration of didanosine buffered tablet formulation with MYTENOTRIN should be under fasted conditions (see section 4.5).

Co-administration of MYTENOTRIN 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 MYTENOTRIN should be monitored for MYTENOTRIN-associated adverse events.

MYTENOTRIN should be discontinued in patients who develop MYTENOTRIN-associated adverse events (see section 4.8).

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

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of MYTENOTRIN 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.

Lipodystrophy and metabolic abnormalities:

Redistribution/accumulation of body fat including central obesity, dorsocervical 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 pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such a 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 disease should be instituted or continued, and ART continued.

Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS.

Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis:

Although the 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.

Bone effects:

During therapy with MYTENOTRIN 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 was not 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.

Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomised controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients. These BMD decreases generally improved after treatment discontinuation.

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were also observed. In a pre-exposure trial of men having sex with men (MSM), a sub study of 503 subjects found mean changes from baseline in BMD ranging from -0,4 % to -1,0 % across total hip, spine, femoral neck, and trochanter in the MYTENOTRIN group compared with the placebo group. Bone fractures were reported in 1,7 % of the MYTENOTRIN group compared with 1,4 % in the placebo group. No correlation between BMD and fractures was noted. A pre-exposure study in heterosexual couples where one of the partners was HIV-1 infected, found similar fracture rates between treatment and placebo groups (0,8 % and 0,6 %, respectively). No BMD evaluations were conducted during this trial.

In other studies (prospective and cross sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor.

Overall in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long-term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures.

Cases of osteomalacia, which can manifest as persistent or worsening bone pain and, which can infrequently contribute to fractures, have been reported in association with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8).

Opportunistic infections:

Patients receiving MYTENOTRIN should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including MYTENOTRIN, does not prevent the risk of transmission of HIV-1 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 MYTENOTRIN for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because MYTENOTRIN 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 gonorrhoea).
- Inform uninfected individuals about and support their efforts in reducing sexual risk behaviour.

Use MYTENOTRIN 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 MYTENOTRIN, because MYTENOTRIN alone does not constitute a complete treatment regimen for HIV-1 treatment. Therefore, care should be taken to avoid MYTENOTRIN 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 of infection. Prior to initiating MYTENOTRIN 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 MYTENOTRIN 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 MYTENOTRIN dosing schedule. The effectiveness of MYTENOTRIN in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable medicine levels in clinical trials.

Early virologic failure:

Clinical trials in HIV-1 infected patients 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.

Geriatric use:

Clinical studies of emtricitabine (200 mg) or tenofovir DF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, 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 therapy.

Lactose intolerance:

MYTENOTRIN contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take MYTENOTRIN.

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been conducted using MYTENOTRIN tablets.

MYTENOTRIN: The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when 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 with other medicines is low.

MYTENOTRIN 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 observed. However, co-administration of MYTENOTRIN with medicines that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the co-administered medicines.

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

No clinically significant interactions have been observed between emtricitabine and famciclovir, indinavir, zidovudine, stavudine, and tenofovir disoproxil fumarate (see Tables 2 and 3). Similarly, no clinically significant interactions have been observed between tenofovir disoproxil fumarate and abacavir, adefovir dipivoxil, ribavirin, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, and saquinavir/ritonavir in studies conducted in healthy volunteers (see Tables 4 and 5).

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	⇔	⇔	↑ 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 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 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1 250 twice daily X 14 days	2	⇔	⇔	
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]	Atazanavir/Ritonavir 300/100 once daily x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 253 (↓ 42 to ↓ 3)	↓ 233 (↓ 46 to ↑ 10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily x 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily X 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Methadone[4]	40 to 110 once daily x 14 days[5]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1 250 twice daily x 14 days	29	⇔	⇔	⇔
Oral Contraceptives[6]	Ethinyl oestradiol 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) ⇔	↑ 297 (↑ 12 to ↑ 48) ⇔	↑ 477 (↑ 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 exposures were equivalent when dosed alone or with tenofovir DF.

5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

6. Ethinyl estradiol 0,035 mg and 17-deacetylnorgestimate.

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.

Following multiple dosing to HIV negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant interactions between these medicines and tenofovir disoproxil fumarate. Co-administration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 6 summarises the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown.

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 capsules				
400 once, fasted	With food, 2 hr 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 hr 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 section 4.4 regarding use of didanosine with tenofovir.
2. Administration with food was with a light meal (~ 373 kcal, 20 % 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 MYTENOTRIN in pregnancy and lactation has not been established (see section 4.3).

Women of childbearing potential / Contraception in males and females

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

Pregnancy

There are no adequate and well-controlled studies in pregnant women. MYTENOTRIN should not be used in pregnancy (see section 4.3).

Breastfeeding

Nursing Mothers: HIV-infected mothers should not breastfeed their infants, to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. It is not known whether emtricitabine is excreted in human milk. **Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving MYTENOTRIN.**

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Side effects have been reported for Emtricitabine and Tenofovir Disoproxil Fumarate:

Blood and lymphatic system disorders:

Frequent: Neutropenia.

Less frequent: Anaemia.

Immune system disorders:

Frequent: Allergic reaction.

Metabolism and nutrition disorders:

Frequent: Hypertriglyceridaemia, hyperglycaemia, hypophosphataemia.

Less frequent: Lactic acidosis, hypokalaemia.

Psychiatric disorders:

Frequent: Abnormal dreams, insomnia.

Nervous system disorders:

Frequent: Dizziness, headache.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, flatulence, dyspepsia, abdominal pain, lipase elevation, amylase elevation.

Less frequent: Pancreatitis.

Hepatobiliary disorders:

Frequent: Hyperbilirubinaemia, increased liver enzymes (including increased AST, increased ALT and/or gamma GT).

Less frequent: Hepatitis, hepatic steatosis.

Skin and subcutaneous tissue disorders:

Frequent: Rash event, (rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and skin discolouration).

Less frequent: Angiodema.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Creatine kinase elevation, bone mineral density decreased.

Less frequent: Myopathy, osteomalacia (manifested as bone pain and infrequently contributing to fractures), rhabdomyolysis, muscular weakness.

Renal and urinary disorders:

Less frequent: Increased creatinine, renal insufficiency, renal failure (acute and chronic), Fanconi syndrome, proximal renal 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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 DF, a four-hour haemodialysis session removed only approximately 10 % of the administered tenofovir dose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class: A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations

ATC code: J05AR03

Mechanism of action:

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'-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir disoproxil fumarate: 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.

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.

In a clinical study of treatment-naïve patients (emtricitabine + tenofovir + efavirenz versus zidovudine + lamivudine + efavirenz), resistance analysis was performed on HIV isolates from all virologic failure patients with > 400 copies/mL of HIV-1 RNA at week 144 or early discontinuations. Development of efavirenz resistance-associated mutations occurred most frequently and was similar between the treatment arms.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analysed subject isolates in the emtricitabine + tenofovir DF group and in 10/29 analysed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of this study, no subjects have developed a detectable K65R substitution in their HIV-1 as analysed through standard genotypic analysis.

The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/12 (17 %) analysed patient isolates in the emtricitabine + tenofovir DF group and in 7/22 (32 %) analysed patient isolates in the zidovudine/lamivudine group.

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).

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral medicines. In a clinical study, viral isolates from 6/16 (37,5 %) treatment-naïve patients with virological failure showed > 20-fold reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due

to M184V/I mutations in the HIV RT gene.

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

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral medicines. In treatment-naïve patients, 8/47 (17 %) isolates from patients on tenofovir + lamivudine + efavirenz through week 144 showed > 1,4-fold (median 3,7) reduced susceptibility in cell culture to tenofovir. In treatment-experienced patients, 14/304 (5 Studies 902 and 907) isolates from patients failing tenofovir through week 96 showed > 1,4-fold (median 2,7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

iPrEx Trial: In a clinical study of HIV-1 seronegative men who have sex with men, no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 48 subjects in the emtricitabine and tenofovir DF group and 83 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be HIV-1 infected at time of enrolment. The M184V/I substitutions associated with resistance to emtricitabine were observed in 3 of the 10 subjects (2 of 2 in the emtricitabine/tenofovir DF group and 1 of 8 in the placebo group) who were HIV-1 positive at time of enrolment. One of the two subjects in the emtricitabine/tenofovir DF group harboured wild type virus at enrolment and developed the M184V substitution 4 weeks after enrolment. The other subject had indeterminate resistance at enrolment but was found to have the M184I substitution 4 weeks after enrolment.

Partners PrEP Trial: In a clinical study of HIV-1 seronegative partners of heterosexual couples of whom one of the partners was HIV-1 infected, no variants expressing amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 12 subjects in the emtricitabine/tenofovir DF group, 15 subjects in the tenofovir DF group, and 51 subjects in the placebo group. Fourteen subjects were observed to be HIV-1 infected at the time of enrolment (3 in the emtricitabine/tenofovir DF group, 5 in the tenofovir DF group, and 6 in the placebo group). One of the three subjects in the emtricitabine/tenofovir DF group who was infected with wild type virus at enrolment selected an M184V expressing virus by week 12. Two of the five subjects in the tenofovir DF group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at

enrolment developed a K65R substitution by week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions upon seroconversion at week 60, although baseline virus was not genotyped and it is unclear if the resistance emerged or was transmitted. Following enrolment, 4 subjects (2 in the tenofovir DF group, 1 in the emtricitabine/tenofovir DF group, and 1 in the placebo group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to non-nucleoside reverse transcriptase inhibitors but have not been associated with tenofovir or emtricitabine and may have been present in the infecting virus.

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 cell culture 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.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility in vitro to didanosine, stavudine, tenofovir, zidovudine, and 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 substitutions 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 (N = 20) whose HIV-1 expressed a mean of 3’ zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, 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.

Antiviral Activity

Emtricitabine and tenofovir disoproxil fumarate:

In combination studies evaluating the in-cell culture antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

5.2 Pharmacokinetic properties

Adults

MYTENOTRIN: One combination tablet was bioequivalent to one emtricitabine capsule (200 mg) plus one tenofovir disoproxil fumarate tablet (300 mg) following single-dose administration to fasting healthy subjects (N = 39).

Emtricitabine:

The pharmacokinetic properties of emtricitabine are summarised in Table 7. Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. *In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 to 200 µg/mL. 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 7. Following oral administration of tenofovir, maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hours. In cell culture binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/mL. Approximately 70 to 80 % of the intravenous dose of tenofovir is recovered as unchanged medicine in the urine. Tenofovir is eliminated by a combination of

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

Table 7

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 ± 0,724	0,30 ± 0,09
AUC[3] (µg·hr/mL)	10,0 ± 3,124	2,29 ± 0,69
CL/F[3] (mL/min)	302 ± 94	1043 ± 115
CLrenal[3] (mL/min)	213 ± 8	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

The combination tablet may be administered with or without food. Administration of the combination tablet following a high fat meal (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. In previous safety and efficacy studies, tenofovir was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when the combination tablet was administered with either a high fat or a light meal.

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 section 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 MYTENOTRIN not be used in patients with creatinine clearance < 50 mL/min or in patients with end-stage renal disease requiring dialysis (see section 4.3 and 4.4).

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

Patients with hepatic impairment

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. The pharmacokinetics of MYTENOTRIN 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Film-coat:

FD & C Blue # 2

Hypromellose

Titanium dioxide

Triacetin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ˚C.

Store in the original container.

Do not remove from the carton until required for use.

6.5 Nature and contents of container

MYTENOTRIN is packed in high density polyethylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene (PP) screw closure with desiccant in 28's, 30's and 100's pack, in a carton.

MYTENOTRIN is packed in high density polyethylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene (PP) screw closure with desiccant in 28's, 30's and 100's pack.

*Not all pack sizes may be marketed

MYTENOTRIN is packed in a high-density polyethylene blue opaque HDPE bottle with a blue opaque polypropylene (PP) closure and with desiccant in 28's and 30's pack, in a carton.

MYTENOTRIN is packed in a high-density polyethylene blue opaque HDPE bottle with a blue opaque polypropylene (PP) closure and with desiccant in 28's and 30's pack.

* Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Kempton Park

Gauteng, 1601

Tel. no.: +27 11 451 1300

8 REGISTRATION NUMBERS

51/20.2.8/0711

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 April 2020

10 DATE OF REVISION OF THE TEXT

05 November 2024