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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ELTENO TABLETS (film coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains efavirenz 600 mg, lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg.

Contains sugar: 304,50 mg lactose monohydrate

For the full list of excipients, see section 6.1.

WARNING

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

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

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3. PHARMACEUTICAL FORM

White to off-white, capsule shaped, biconvex film coated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELTENO TABLETS is indicated for the treatment of HIV-1 infected adults over 18 years of age who have been treated and stabilised on a combination of the 3 antiretrovirals contained in **ELTENO TABLETS**, administered as separate formulations and at similar dosages as contained in **ELTENO TABLETS**.

4.2 Posology and method of administration

Posology

Adults*:*

The recommended dose of **ELTENO TABLETS** is one tablet taken orally once daily.

ELTENO TABLETS should be taken on an empty stomach, since food may increase efavirenz exposure and this may cause an increase in the frequency of adverse reactions. In order to improve the tolerability to efavirenz with respect to undesirable effects on thenervous system, it is recommended that **ELTENO TABLETS** be taken at bedtime.

Children and adolescents*:*

ELTENO TABLETS is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy (see section 4.3)

Renal impairment*:*

ELTENO TABLETS is not recommended for patients with moderate to severe impairment of renal function (creatinine clearance < 50 mℓ/min)

Missed doses*:*

It is important to take **ELTENO TABLETS** on a regular dosing schedule. Patients should be told that if they forget to take **ELTENO TABLETS**, they should take the missed dose right away, unless it is less

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than 12 hours until the next day's dose. In this case, patient should be told not to take the missed dose and to take the next dose at the usual time.

Discontinuation of therapy*:*

Where discontinuation of treatment with one of the components of **ELTENO TABLETS** is indicated or where dose modification is required, separate preparations of efavirenz, lamivudine and tenofovir are available. Please refer to the individual package inserts of these medicines.

If therapy of **ELTENO TABLETS** is discontinued, consideration should be given to the long half-life of efavirenz and long intracellular half-lives of tenofovir and lamivudine. Because of interpatient variability in these parameters and concerns regarding development of resistance, HIV treatment guidelines should be consulted.

Method of administration

Oral use

4.3 Contraindications

ELTENO TABLETS is contra-indicated in patients:

- With previously demonstrated hypersensitivity to efavirenz, lamivudine or tenofovir or any of the other components of the product.
- Who are pregnant or breastfeeding (see section 4.6).
- With moderate to severe impairment of renal function (creatine clearance < 50 mℓ/min) (see section 4.4 and 4.2).
- With moderate to severe uncontrolled renal failure.
- Who are receiving treatment with other efavirenz-containing products, or other lamivudine-containing products or other tenofovir-containing products.
- Who are receiving treatment with adefovir dipivoxil (see section 4.5).
- Who are concurrently receiving treatment with astemizole, cisapride, midazolam, triazolam or ergot derivatives (e.g. ergotamine, dihydroergotamine, ergonovine and methylergonovine), or

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zalcitabine because competition for CYP3A4 by the efavirenz in **ELTENO TABLETS** could result in inhibition of the metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g., cardiac dysrhythmias, prolonged sedation or respiratory depression) (see section 4.5).

- Who are using herbal preparations containing St John's Wort (*Hypericum perforatum*) due to the risk associated with decreases plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).
- Who are concurrently using voriconazole, since efavirenz significantly decreases voriconazole plasma concentrations, while voriconazole significantly increases efavirenz plasma concentrations. Since **ELTENO TABLETS** is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore voriconazole and **ELTENO TABLETS** must not be co-administered (see section 4.5).
- With severe hepatic impairment (Child-Pugh class C).
- A history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART).
- Children less than 18 years due to lack of data on safety and efficacy.

4.4 Special warnings and precautions for use

- There are no study results demonstrating the effect of **ELTENO TABLETS** on clinical progression of HIV-1.
- Co-administration with related medicines (see section 4.5): as a fixed dose combination, **ELTENO TABLETS** should not be administered concomitantly with other medicines containing any of the same active components, namely: efavirenz, lamivudine or tenofovir DF.

Drug induced liver failure:

There is some evidence that efavirenz is associated with three clinical pathological patterns of drug induced liver failure in HIV positive patients of which the sub massive necrosis histological pattern seems to be associated with a high morbidity/mortality risk and may present many months after

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therapy has been initiated or even stopped.

Risk factors include:

- younger age
- CD4+ counts ≥ 350 cells/µl
- female gender.

Patients on **ELTENO TABLETS** or efavirenz containing antiretroviral treatment (ART) should be regularly monitored for jaundice (including a laboratory bilirubin and liver enzymes) and bleeding tendencies.

Early detection and treatment of the liver failure and the immediate discontinuation of **ELTENO TABLETS** or efavirenz containing medicines should be stressed. Patients who discontinued treatment with **ELTENO TABLETS** should be followed up for symptoms/signs of liver failure for up to 12 months.

ELTENO TABLETS is not recommended in patients with moderate to severe hepatic impairment because there are insufficient data to determine whether dose adjustments are required.

The safety and efficacy of ELTENO TABLETS in patients with both HIV and hepatitis B virus infection have not been established.

Lactic Acidosis/hyperlactataemia

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

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

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

– **Lactate 2 – 5 mmol/ℓ with minimum symptoms:** switch to agents that are less likely to cause

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lactic acidosis.

- **Lactate 5 – 10 mmol/ℓ with symptoms and or with reduced 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 **ELTENO TABLETS** to patients with known factors for liver disease.

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

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 (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 or symptoms.

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

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

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

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package

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inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue **ELTENO TABLETS** should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Discontinuation of **ELTENO TABLETS** therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis.

Renal impairment:

Lamivudine and tenofovir, two of the active ingredients in **ELTENO TABLETS**, are principally eliminated by the kidney .**ELTENO TABLETS** should not be administered to patients with creatinine clearance < 50 mℓ/min and serum phosphate < 0,32 mmol/ℓ.

There have been reports of renal impairment including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) in association with the use of tenofovir DF (see sections 4.3 and 4.8).

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with ELTENO TABLETS. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment (see section 4.3 and 4.4).

The use of **ELTENO TABLETS** should be avoided in patients who are concurrently taking or who have recently taken a nephrotoxic medicine.

Liver disease

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

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discontinuation of treatment must be considered.

Psychiatric symptoms:

Psychiatric adverse experiences have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at a greater risk of these serious psychiatric adverse reactions. Severe depression is more common in those with a history of depression. There have been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to consider alternative treatment (see section 4.8).

Nervous system symptoms:

Central nervous system symptoms may occur in a significant number of patients. These symptoms include dizziness, insomnia, impaired concentration, somnolence, abnormal dreams and hallucinations. Other reported symptoms are euphoria, confusion, agitation, amnesia, stupor, abnormal thinking and depersonalisation. The majority of these symptoms are mild-moderate; symptoms are severe in 2,0 % of patients. Overall 2,1 % of patients may discontinue therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2-4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranges from 5 % to 9 %in patients treated with regimens containing efavirenz. Patients should be informed that these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of the less frequent psychiatric symptoms (see section 4.4).
Dosing at bedtime may improve the tolerability of these nervous symptoms (see section 4.2).

Patients receiving **ELTENO TABLETS** should be alerted to the potential for additive central nervous system effects when **ELTENO TABLETS** is used concomitantly with alcohol or psychoactive medicines.

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Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

***Seizures*:**

Convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Caution must be taken in any patient with a history of seizures.

Pancreatitis

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

Medicine Interactions (*see INTERACTIONS*)

When tenofovir DF is administered with didanosine, the C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increases significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy.

Co-administration of didanosine buffered tablet formulation with ELTENO TABLETS is not recommended.

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

Skin rash:

Mild-to-moderate rash, which usually resolves with continued treatment, has been observed with efavirenz use. Treatment with appropriate antihistamines and/or corticosteroids may improve tolerability and hasten resolution of symptoms. Treatment with **ELTENO TABLETS** should be

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discontinued in patients who experience severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with **ELTENO TABLETS** is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of medicine resistant virus (see section 4.8).

Liver enzymes:

Monitoring of liver enzyme levels is recommended in patients with known or suspected history of hepatitis B or C infection and in patients treated with other medicines associated with hepatic toxicity. The benefit of continued therapy with **ELTENO TABLETS** has to be weighed against the unknown risks of significant hepatic toxicity in patients who show persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range (see **Side-Effects**).

Because of the extensive cytochrome P450 mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering **ELTENO TABLETS** to these patients.

***Bone effects*:**

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

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

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Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

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Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, it presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic

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diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Cholesterol:

Monitoring of cholesterol and triglyceride levels should be considered in patients treated with **ELTENO TABLETS** (see section 4.8).

Paediatric use

Safety and effectiveness of **ELTENO TABLETS** in children have not been established.

Use in the Elderly:

Clinical studies of efavirenz, lamivudine and tenofovir such as contained in **ELTENO TABLETS**, did not include sufficient numbers of individuals older than 65 years to establish whether they respond differently from younger subjects. Generally, caution is required when doses are selected for elderly patients, bearing in mind the greater frequency of decreased liver, kidney and cardiac function, and of concomitant disease or medicinal therapy.

Patients should be alerted to the potential for additive central system effects when **ELTENO TABLETS** is used concomitantly with alcohol or psychoactive medicines.

Opportunistic infections:

Patients receiving **ELTENO TABLETS** 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

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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 **ELTENO TABLETS**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Excipients

Lactose:

ELTENO TABLETS contains lactose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicines and other forms of interaction

No medicine interaction studies have been conducted using **ELTENO TABLETS**. As **ELTENO TABLETS** contains efavirenz, lamivudine and tenofovir DF, any interactions that have been identified with these medicines individually may occur with **ELTENO TABLETS**.

Important medicine interaction information for **ELTENO TABLETS** are summarised in Tables 1, 2 and 3. The medicine interactions described are based on studies conducted with efavirenz, lamivudine or tenofovir DF as individual agents or are potential medicine interactions. The tables include potentially significant interactions, but are not all inclusive.

As a fixed combination, **ELTENO TABLETS** should not be administered concomitantly with other medicines containing any of the components efavirenz, lamivudine or tenofovir DF.

Lamivudine:

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Administration of co-trimoxazole results in a 40 % increase in lamivudine exposure, because of the

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trimethoprim component; the sulphamethoxazole component does not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole. When concomitant administration with co-trimoxazole is warranted patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of *Pneumocystis jirovecii (carinii)* pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicines (e.g. ranitidine, cimetidine) and the nucleoside analogues (e.g. didanosine, zidovudine) are eliminated only in part by this mechanism and are shown not to interact with lamivudine.

A modest increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however, overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine (see Pharmacokinetic properties).

Lamivudine metabolism does not involve CYP3A, making interactions with medicines metabolised by this system (e.g. protease inhibitors) unlikely.

Tenofovir disoproxil fumarate: Since tenofovir are primarily eliminated by the kidneys, co-administration of **ELTENO TABLETS**with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir,and/or other renally eliminated medicines. Some examples include, but are not limited toaciclovir, adefovir dipivoxil, cidofovir, ganciclovir, valaciclovir, and valganciclovir.

Co-administration of tenofovir DF with didanosine results in changes in the pharmacokinetics that may be of clinical significance. Table 1 summarises the effects of tenofovir DF on the pharmacokinetics of didanosine. Co-administration of tenofovir DF and didanosine is not recommended.

Concomitant dosing of tenofovir DF with didanosine buffered tablets or enteric-coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated

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capsules were administered with tenofovir DF, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 1.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 **WARNINGSAND SPECIAL PRECAUTIONS** 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

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Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving either atazanavir or lopinavir/ritonavir with tenofovir DF should be monitored for tenofovir-associated adverse events. **ELTENO TABLETS** should be discontinued in patients who develop tenofovir-associated adverse events (For atazanavir dosing adjustment recommendations see Table 3).

No clinically significant medicine interactions have been observed between emtricitabine and tenofovir, indinavir, stavudine, tenofovir DF and zidovudine. Similarly, no clinically significant interactions have been observed between tenofovir DF and abacavir, adefovir dipivoxil, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin and saquinavir/ ritonavir in studies conducted in healthy volunteers.

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy, oral contraceptives or single dose of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant medicine interaction between these agents and tenofovir DF.

Renally eliminated medicines:

Since tenofovir is primarily eliminated by the kidneys, co-administration of **ELTENO TABLETS** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or the co-administered medicines.

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

Efavirenz: Efavirenz has been shown in *vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19, and 3A4 isozymes in

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the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with medicines primarily metabolised by these isozymes may result in altered plasma concentrations of the co-administered medicine. Therefore, appropriate dose adjustments may be necessary for these medicines.

Medicines that induce CYP3A4 activity (e.g., phenobarbital, rifampicin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Efavirenz exposure may also be altered when given with certain foods (e.g. grapefruit juice) which affect CYP3A4 activity.

Table: 2

Medicines that are contra-indicated or not recommended for use With ELTENO TABLETS

Medicine Class: **Medicine Name**	**Clinical Comment**
Antifungal: voriconazole	CONTRA-INDICATED because efavirenz significantly decreases voriconazole plasma concentrations and co-administration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side-effects.
Antihistamine: astemizole	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Anti-migraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRA-INDICATED due to potential for serious and/ or life threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.
Anti-retroviral: efavirenz, emtricitabine, tenofovir DF, lamivudine	Not for use with **ELTENO TABLETS** because the active ingredients- efavirenz, lamivudine and tenofovir DF are components of **ELTENO TABLETS**. Lamivudine is similar to

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	emtricitabine.
Benzodiazepines: midazolam, triazolam	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
GI motility agent: cisapride	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Neuroleptic: pimozide	CONTRA-INDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
St. John's wort (*Hypericum perforatum*)	NOT RECOMMENDED: Expected to substantially decrease plasma levels of efavirenz; the effect is due to an induction of CYP3A4 and may result in a loss of therapeutic effect and loss of resistance.

Table: 3

Established and Other Potentially Significant[1] Medicine Interactions:

Alteration in Dose or Regimen May Be Recommended Based on Medicine Interaction Trials or Predicted Interaction

Concomitant Medicine Class: Medicine Name	**Effect**	**Clinical Comment**
Antiretroviral agents		
Protease inhibitor: Amprenavir	↓ amprenavir concentration	Efavirenz has the potential to decrease serum concentrations of amprenavir
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and **ELTENO TABLETS** with respect to safety and efficacy have not been established.

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		Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when **ELTENO TABLETS** is administered with fosamprenavir once daily. No change in the ritonavir dose is required when **ELTENO TABLETS** is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when **ELTENO TABLETS** is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Plasma concentration of atazanavir was decreased by both efavirenz and tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with **ELTENO TABLETS**. Therefore co-administration of **ELTENO TABLETS** and atazanavir is not recommended due to concerns regarding decreased atazanavir concentration.
Protease inhibitor: Indinavir	↓ indinavir concentration.	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz
Protease inhibitor:	↓ lopinavir	A dose increase of lopinavir/ritonavir to

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Lopinavir/ritonavir	concentration ↑ tenofovir concentration	600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment- experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **Patients should be monitored for tenofovir-associated adverse events. ELTENO TABLETS should be discontinued in patients who develop tenofovir-associated adverse events.**
Protease inhibitor: Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours was co-administered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (e.g. dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when **ELTENO TABLETS** is used in combination with ritonavir.
Protease Inhibitor: Saquinavir	↑ saquinavir concentration	Should not be used as sole protease inhibitor in combination with **ELTENO TABLETS**
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy.

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		Co-administration of ELTENO TABLETS and didanosine is not recommended.
Other agents		
Anticoagulant: Warfarin	↑ or↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for **ELTENO TABLETS**. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant concentration ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant : Sertraline.	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Antifungals: Itraconazole Ketoconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration ↓ ketoconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered. Medicine interaction studies with **ELTENO TABLETS** and ketoconazole have not been conducted. Efavirenz has the potential to decrease plasma concentrations of ketoconazole.
Anti-infective: Clarithromycin.	↓ clarithromycin concentration ↑14-OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of

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		ELTENO TABLETS is recommended when given with clarithromycin. Alternative to clarithromycin such as azithromycin should be considered. Other macrolide antibiotics, such as, erythromycin, have not been studied in combination with **ELTENO TABLETS**.
Antimycobacterial: Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50 %. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimycobacterial: Rifampicin	↓ efavirenz concentration	Rifampicin reduced efavirenz AUC by 26 % and C_{max} by 20 % in 12 uninfected volunteers. The dose of efavirenz must be increased to 800 mg/day when taken with rifampicin.
Calcium channel blockers: Diltiazem Others (e.g., felodipine, nifedipine, nicardipine, verapamil)	↓ diltiazem concentration ↓ desacetyl diltiazem concentration ↓ N-monodesmethyl diltiazem concentration ↓ calcium channel blocker.	Diltiazem dose adjustments should be guided by clinical response. No dose adjustment of **ELTENO TABLETS** is necessary when administered with diltiazem. No data are available on potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A4 enzymes. The potential exists for

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		reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response
HMG-CoA reductase inhibitors: Atorvastatin, Pravastatin, Simvastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin concentration	Plasma concentrations of atorvastatin, pravastatin and simvastatin decreased with efavirenz. Consult the full package inserts for the HMG-CoA reductase inhibitor for guidance on individualising the dose.
Narcotic analgesic: Methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-1 infected individuals with a history of injection medicine use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Oral contraceptives: Ethinyl oestradiol	↑ ethinyl oestradiol concentration	Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised. A reliable method of barrier contraception should be used in addition to oral contraceptives.

1This table is not all inclusive

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Medicine interaction studies were performed with efavirenz and other medicines likely to be co-administered or medicines commonly used as probes for pharmacokinetic interaction. There was no clinically significant interaction observed between efavirenz and zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine or paroxetine. Single doses of famotidine or an aluminium and magnesium antacid with simethicone had no effects on efavirenz exposures.

Efavirenz Assay Interference

Cannabinoid Test Interaction: Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been observed in non-HIV-infected volunteers receiving efavirenz when the Microgenics Cedia DAU Multi-Level THC assay was used for screening. Negative results were obtained when more specific confirmatory testing was performed with gas chromatography/mass spectrometry.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of **ELTENO TABLETS** during pregnancy is contra-indicated as safety and efficacy have not been established (see section 4.3).

The use of efavirenz during pregnancy is contra-indicated, as teratogenicity has been noted. Malformations have been observed in foetuses from efavirenz-treated monkeys that received doses which resulted in plasma-efavirenz concentrations similar to those in humans given 600 mg/day.

Barrier contraception should always be employed in combination with other contraceptive methods (e.g., oral or other hormonal contraceptives) while on therapy with **ELTENO TABLETS**. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of **ELTENO TABLETS** is recommended.

Women of childbearing potential should undergo pregnancy testing prior to initiation of treatment with **ELTENO TABLETS** (see section 4.3).

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Breastfeeding

Breastfeeding mothers: HIV-infected mothers should not breastfeed their infants. It is not known whether efavirenz, lamivudine or tenofovir are excreted in human milk. Due to the potential for HIV transmission and the potential for serious adverse reactions in breastfed infants, **mothers should be instructed not to breastfeed if they are taking ELTENO TABLETS**.

4.7 Effects on ability to drive and use machines

ELTENO TABLETS may lead to dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that, if they develop these symptoms, they should keep away from potentially hazardous tasks, such as driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

EFAVIRENZ (600 mg):

MedDRA System organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Less frequent	Allergic reaction, immune-allergic liver injury/failure
Metabolism and nutrition disorders	Less frequent	Anorexia, raised serum-cholesterol and triglyceride concentrations, weight gain and weight loss, redistribution/accumulation of body fat, increased appetite.
Psychiatric disorders	Frequent	Aggravated depression.
	Less frequent	Abnormal dreams, anxiety, agitation, amnesia, apathy, confusion, emotional lability, euphoria, hallucination, insomnia, somnolence, delusions, inappropriate behaviour, severe acute depression

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		(including suicide ideation and attempt), neurosis, paranoia, apathy.
Nervous system disorders	Frequent	Dizziness, headache.
	Less frequent	Impaired concentration, abnormal coordination, ataxia, convulsions, hypoaesthesia, neuralgia, paraesthesia, peripheral neuropathy, speech disorder, tremor, vertigo, syncope
Eye disorders	Less frequent	Abnormal vision
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Palpitations and tachycardia
Respiratory, thoracic and mediastinal disorders	Less frequent	Asthma, upper respiratory tract infection, sinusitis
Gastrointestinal disorders	Frequent	Nausea
	Less frequent	Vomiting, diarrhoea, dyspepsia, abdominal pain, taste perversion, gastritis, gastroenteritis, gastro-oesophageal reflux, constipation, malabsorption.
Hepato-biliary disorders	Less frequent	Hepatitis, increased hepatic enzymes, hepatic failure.
Skin and subcutaneous tissue disorders	Frequent	Rash and increased swelling
	Less frequent	Erythema multiforme, Stevens-Johnson syndrome, alopecia, skin exfoliation, urticaria, nail disorders, skin discolouration, acne, eczema, folliculosis, seborrhea, photoallergic dermatitis.
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, myalgia, myopathy

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Reproductive system and breast disorders	Less frequent	Impotence, decreased libido, increased libido, gynaecomastia
General disorders and administrative site conditions	Frequent	Fatigue
	Less frequent	Asthenia, malaise, hot flushes, pain, influenza-like symptoms

LAMIVUDINE (300 mg):

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequent	Neutropenia, anaemia (both occasionally severe), thrombocytopenia, pure red cell aplasia.
Nervous system disorders	Frequent	Headache, insomnia
	Less frequent	Peripheral neuropathy (or paraesthesia)
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, nasal symptoms
Gastrointestinal disorders	Frequent	Nausea, vomiting, abdominal cramps, diarrhoea
	Less frequent	Pancreatitis, elevations in serum amylase
Hepatobiliary disorders	Less frequent	Transient elevations in liver enzymes (AST,ALT), hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, alopecia
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, muscle disorders
	Less frequent	Rhabdomyolysis
General disorders and administration site conditions	Frequent	Fatigue, malaise, fever

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TENOFOVIR (300 mg):

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequency unknown	Neutropenia, haematuria
Immune system disorders	Less frequent	Allergy, allergic reaction
Metabolism and nutritional disorders	Frequent	Hypophosphataemia.
	Less frequent	Lactic acidosis, usually associated with severe hepatomegaly and steatosis, hypertriglyceridaemia, hyperglycaemia..
Psychiatric disorders	Frequency unknown	Depression, anxiety
Nervous system disorders	Frequent	Headache, dizziness, peripheral neuropathy (including peripheral neuritis, neuropathy)
Respiratory, thoracic and mediastinal disorders	Less frequent	Chest pain, pneumonia, dyspnoea
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea, abdominal pain, flatulence, dyspepsia and anorexia
	Less frequent	Raised serum amylase concentration, increased amylase pancreatitis.
Hepatobiliary disorders	Frequent	Raised liver enzymes and hepatitis
Skin and subcutaneous tissue disorders	Less frequent	Skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash).

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Musculoskeletal and connective tissue disorders	Less frequent	Back pain, arthralgia, myalgia, myopathy, osteomalacia (both associated with proximal renal tubulopathy), increased creatine kinase levels.
Renal and urinary disorders	Less frequent	Increased creatinine nephritis, nephrogenic diabetes insipidus, proximal tubulopathy, proteinuria, renal impairment, renal failure, renal insufficiency, acute renal failure, acute tubular necrosis, and effects on the renal proximal tubules, including Fanconi syndrome, polyuria, interstitial nephritis (including acute cases).
General disorders	Less frequent	Fever, sweating, weight loss, asthenia

Combination antiretroviral therapy

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure (CART). The frequency

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of which is unknown.

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 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

In the event of overdose, the patient must be monitored for evidence of toxicity, and standard supportive treatment given as necessary.

Efavirenz:

Overdose may cause nervous system symptoms and involuntary muscle contractions. Treatment of efavirenz overdose should consist of general supportive measures. These should include vital sign monitoring and observation of the patient's clinical status. Activated charcoal may be administered to aid removal of unabsorbed medicine. There is no specific antidote for overdose with efavirenz. Dialysis is unlikely to significantly remove efavirenz from the blood, since the medicine is highly protein bound.

Lamivudine:

If overdosage occurs the patient should be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of over dosage, although this has not been studied.

Tenofovir disoproxil fumarate

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

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antimicrobial (Chemotherapeutic) Agents, Antiviral agents

ELTENO TABLETS is a fixed dose combination tablet containing efavirenz,a non-nucleoside reverse transcriptase inhibitor (NNRTI), lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI) and tenofovir disoproxil fumarate (tenofovir DF) a nucleoside reverse transcriptase inhibitor (NRTI).

***Tenofovir disoproxil fumarate*:** Tenofovir disoproxil fumarate is a nucleoside reverse transcriptase inhibitor (NRTI). Tenofovir disoproxil fumarate, also known as tenofovir DF, is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Efavirenz:

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1.Efavirenz diffuses into the cell where it binds adjacent to the active site of reverse transcriptase (RT). This produces a conformational change in the enzyme and inhibits its function. Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 reverse transcriptase (RT) with respect to template, primer or nucleoside triphosphates, with a small component of competitive inhibition. Efavirenz does not inhibit HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ.

Lamivudine:

Lamivudine has selective *in vitro* activity against the replication of HIV-1 and HIV-2, including zidovudine-resistant HIV isolates. Lamivudine is metabolised intracellularly to an active 5'-

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triphosphate metabolite which inhibits both RNA- and DNA-dependent activities of the HIV reverse transcriptase enzyme by termination of the viral DNA chain. Cellular deoxynucleotide metabolism is not affected by lamivudine and lamivudine has only limited effects on mammalian cell and mitochondrial DNA content.

In vitro, the cytotoxic effect of lamivudine on a variety of bone marrow progenitor cells, on peripheral blood lymphocytes and on established monocyte-macrophage and lymphocyte cell lines is low. The *in vitro* therapeutic index of lamivudine is therefore high.

A reduction in the *in vitro* sensitivity of HIV isolates from patients previously treated with lamivudine has been reported. Lamivudine, as well as other medicines against HIV, particularly zidovudine, show additive or synergistic effects on the inhibition of HIV replication in cell culture, when used concomitantly.

Tenofovir disoproxil fumarate:

Tenofovir DF, a NRTI, is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate and 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 through competing with the natural substrate deoxyadenosine 5'-triphosphate. After incorporation into DNA, the DNA chain is terminated. Tenofovir diphosphate weakly inhibits mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral activity:

Efavirenz, lamivudine and tenofovir disoproxil fumarate:

In combination studies that evaluated the antiviral activity*in vitro* of lamivudine, efavirenz together and tenofovir together,synergistic antiviraleffects were observed.

Resistance:

Efavirenz:

HIV-1 isolates with reduced susceptibility to efavirenz (more than 380-fold increase in IC_{90} value) compared to baseline can emerge *in vitro*. Phenotypic changes in evaluable HIV-1 isolates and genotypic changes in plasma virus from selected patients treated with efavirenz in combination with

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IDV or ZDV plus lamivudine were monitored. One or more RT mutations at amino acid positions 100, 101, 103, 108, 190 and 225 were observed in all patients with a frequency of at least 10 % compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagines) was the most frequently observed (greater or equal to 90 %). A mean loss in susceptibility (IC_{90}) to efavirenz of 47-fold was observed in 26 clinical isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9 to greater than 312-fold increase in IC_{90}) were observed for these isolates *in vitro* compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes as associated with efavirenz therapy has not been established.

Lamivudine:

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*.*In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remain, however, not well defined.

Tenofovir disoproxil fumarate:

Isolates of HIV-1 that exhibited reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65Rmutation in reverse transcriptase and demonstrated a reduced susceptibility to tenofovir of between 2- and 4-fold.Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir DF in combination with certain antiretroviral medicines.

Cross-resistance*:*

Efavirenz, lamivudine and tenofovir disoproxil fumarate:

Cross-resistance has been recognised among certain reverse transcriptase inhibitors. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir,

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didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these medicines may therefore develop in patients whose virus harbours the K65Rmutation.

Efavirenz:

Rapid emergence of HIV-1 strains that are cross-resistant to NNRTIs has been observed *in vitro*. Clinical isolates previously characterised as efavirenz-resistant were also phenotypically resistant to nevirapine and delavirdine *in vitro* compared to baseline. Clinically derived ZDV-resistant HIV-1 isolated and tested *in vitro* retained susceptibility to efavirenz. Cross-resistance between efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Lamivudine:

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral medicines. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184VRT mutant shows a < 4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown.

Tenofovir disoproxil fumarate:

HIV-1 isolates from subjects 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.

5.2 Pharmacokinetic properties

Efavirenz:

Absorption:

Peak efavirenz plasma concentrations of 1,6 – 9,1 µM are reached by 5 hours following single oral doses of 100 mg to 1600 mg given to uninfected volunteers. Although dose-related increases in C_{max} and AUC are seen for doses up to 1600 mg, these increases are less than proportional, indicating diminished absorption at higher doses. Steady state plasma concentrations are reached in 6 to 10

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days.

Distribution:

Efavirenz is highly plasma protein bound (approximately 99,5 – 99,75 %) and predominantly to albumin. Cerebrospinal fluid concentrations ranges from 0,26 to 1,19 % (mean 0,69 %) of the corresponding plasma concentrations in HIV-1 infected individuals administered 200 to 600 mg efavirenz once daily for at least one month. This is about three times higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism:

Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. The metabolites are not active against HIV-1. CYP3A4 and CYP2B6 are the major isozymes involved in efavirenz metabolism. Efavirenz, through induction of P450 enzymes, induces its own metabolism.

Elimination:

Efavirenz has a long terminal half-life of 52 – 76 hours and 40 – 55 hours after single and multiple doses, respectively. Subsequent to the administration of a radio-labelled dose, 14 – 34 % of efavirenz is recovered in the urine (mostly as metabolites) and 16 – 61 % is recovered in the faeces (mostly as parent substance).

Lamivudine:

Absorption:

Following oral administration lamivudine is well absorbed from the gastro-intestinal tract. The bioavailability of lamivudine is approximately 80 %. The mean time (T_{max}) to achieve maximum serum concentration (C_{max}) is approximately one hour. C_{max} is approximately 1-1,5 µg/mℓ at therapeutic doses, i.e. at a dose of 4 mg/kg/day given as two 12-hourly doses.

A delay in T_{max} and reduction in C_{max} have been observed when co-administered with food, but no dosage adjustment is needed as lamivudine bioavailability is not altered. Co-administration of zidovudine results in 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety.

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Distribution:

Lamivudine has a mean volume of distribution of 1,3 ℓ/kg. Lamivudine displays linear pharmacokinetics within the therapeutic dose range, and exhibits limited binding to albumin.

Lamivudine crosses the blood-brain barrier and is distributed into the cerebrospinal fluid (CSF) to a limited extent. The true extent or clinical significance of this penetration is not known.

Metabolism and Elimination:

Lamivudine has a mean elimination half-life of 5 to 7 hours. The active metabolite, lamivudine triphosphate, has a prolonged intracellular terminal half-life averaging over 10 hours in peripheral blood lymphocytes. Lamivudine has a mean systemic clearance of approximately 0,32 ℓ/kg/h, predominantly through renal clearance of unchanged lamivudine by active tubular secretion (>70 %) and a minimal (<10 %) amount through hepatic metabolism.

Tenofovir disoproxil fumarate:

Absorption:

Following oral administration of a single 300 mg dose of tenofovir DF to HIV-1 infected patients in the fasting state, maximum tenofovir serum concentrations were achieved in 1,0 ± 0,4 hour (mean ± SD), and C_{max} and AUC values were 296 ± 90 90 ng/mℓ and 2287 ± 685 ng.hr.mℓ respectively.

The oral bioavailability of tenofovir from tenofovir DF in fasted patients is approximately 25 %.

Distribution:

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

Metabolism and elimination:

Approximately 70 – 80 % of the intravenous dose of tenofovir is recovered as unchanged in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion with a renal clearance in adults with normal renal function of 243 ± 33 ml/min (mean ± SD). Following a single oral dose of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours.

Effects of food on oral absorption:

ELTENO TABLETS has not been evaluated in the presence of food. Administration of efavirenz

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tablets with a high fat meal increased the mean AUC and C_{max} of efavirenz by 28 % and 79 % respectively, compared to administration in the fasted state.

Co-administration of lamivudine with food results in a delay of T_{max} and a lower C_{max} (decreased by 47 %). However, the extent (based on the AUC) of lamivudine absorbed is not influenced.

Administration of tenofovir following a high fat meal (~ 700 to 1000 kcal containing 40 to 50 % fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40 % and an increase C_{max} of approximately 14 %. However, administration of tenofovir with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ± 119 ng/mℓ and 3324 ± 1370 ng.h/mℓ following multiple doses of tenofovir 300 mg once daily in the fed state, when meal content was not controlled (see section 4.2).

Special Populations

Paediatric and elderly patients

Efavirenz: Efavirenz has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg.

Lamivudine: In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability is reduced to approximately 65 %, in paediatric patients, with an increased clearance of 0,52ℓ/kg/hr. There are limited pharmacokinetic data for patients < 3 months of age.

Tenofovir disoproxil fumarate: Pharmacokinetic studies of tenofovir DF have not been performed in paediatric patients (less than 18 years).

ELTENO TABLETS is not recommended for paediatric administration.

Pharmacokinetics of efavirenz, lamivudine and tenofovir have not been fully evaluated in the elderly (more than 65 years) (see section 4.3).

Patients with impaired renal function

Efavirenz: The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency, however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

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Lamivudine: Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. A recommended dosage regimen of patients with creatinine clearance below 50 mℓ/min is shown in the dosage section.

Tenofovir Disoproxil Fumarate: The pharmacokinetics of tenofovir DF is altered in patients with renal impairment (see section 4.1 and 4.2). In patients with creatinine clearance less than 50 mℓ/min, C_{max} and $AUC_{0-\infty}$ of tenofovir were significantly increased.

It is recommended that **ELTENO TABLETS** not be used in patients with creatine clearance (CrCL) < 50 mℓ/min and in patients with end-stage renal disease requiring dialysis (see Section 4.3).

Patients with impaired renal function

The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment (See section 4.3). In patients with creatinine clearance < 50 mL/min, Cmax, and AUC0-∞ of emtricitabine and tenofovir were increased. ELTENO TABLETS should not be used in patients with creatinine clearance < 50 mL/min and in patients with end-stage renal disease requiring dialysis (see sections 4.3 and 4.4).

Patients with hepatic impairment

Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see WARNINGS AND PRECAUTIONS, Liver enzymes).

Lamivudine: Data obtained in patients with moderate to severe hepatic impairment shows that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

Tenofovir disoproxil fumarate: The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir DF 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.

ELTENO TABLETS should not be used in patients with severe hepatic impairment (see section 4.1 and 4.3).

S.D.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, poloxamer, hydroxypropyl cellulose, sodium lauryl sulfate, magnesium stearate (vegetable grade) and pregelatinized starch. Tablet film coating consisting of lactose monohydrate, hypromellose, titanium dioxide (C.I. No. 77891) and triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the HDPE containers closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

HDPE Container Pack:

Tablets are packed in 120 ml round white HDPE bottle with 38-400 neck finish closed with 38 mm white polypropylene closure, with pulp and heat seal liner (123 white printed liner). Each container contains 28 or 30 tablets and 2 silica gel sachets. The containers are packed in a pre-printed unit carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd.

Ground Floor, Block 1

S.D.

Bassonia Estate Office Park (East)

1 Cussonia Drive

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Alberton

Gauteng

8. REGISTRATION NUMBER:

49/20.2.8/0224.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 September 2016

10. DATE OF REVISION OF THE TEXT

01 October 2024

S.D.