PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MYLONZA Tablets

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Tenofovir disoproxil fumarate	300 mg
Lamivudine	300 mg

Efavirenz 400 mg

Contains sugar (lactose monohydrate 218 mg)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A white to off-white, film-coated, oval, biconvex, beveled edge tablet debossed with M on one side and TLE on the other side.

Tablet dimensions: 21,4 x 10,8 mm, thickness 8,25 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MYLONZA 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 three antiretrovirals contained in **MYLONZA** administered as separate formulations in similar dosages as contained in **MYLONZA**.

4.2 Posology and method of administration

Posology:

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection. In exceptional circumstances in patients having difficulty in swallowing, **MYLONZA** can be administered following disintegration of the tablet in at least 100 ml of water, orange juice or grape juice.

Adults:

The recommended dose is one **MYLONZA** tablet once daily taken orally on an empty stomach.

It is recommended that Efavirenz be taken on an empty stomach. The increased efavirenz concentrations observed following administration of Efavirenz with food may lead to an increase in frequency of adverse events. In order to improve the tolerability of nervous system undesirable effects, bedtime dosing is recommended.

Special populations

Children and adolescents:

The safety and efficacy of tenofovir disoproxil fumarate in patients under the age of 18 years have not been established. Tenofovir disoproxil fumarate must not be administered to children or adolescents until further data become available describing the safety and efficacy of tenofovir disoproxil fumarate in patients under the age of 18 years. So, **MYLONZA** tablets are not recommended in children and adolescents.

Elderly:

No data are available on which to make a dose recommendation for patients over the age of 65 years.

Adolescents, Children and Infants less than three months of age:

MYLONZA is a fixed medicine combination tablet and the dose cannot be adjusted, therefore **MYLONZA** is not for use in patients less than 18 years of age.

Renal insufficiency*:*

MYLONZA is contraindicated in renal impairment with creatinine clearance < 50 ml/min.

Hepatic impairment:

Tenofovir disoproxil fumarate

No dose adjustment is required in patients with hepatic impairment for tenofovir. However,

MYLONZA should not be used in patients with severe hepatic impairment (see 4.3).

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. However, **MYLONZA** should not be used in patients with severe hepatic impairment (see 4.3).

Efavirenz

Patients with mild to moderate liver disease may be treated with their normally recommended dose of efavirenz. Patients should be monitored carefully for dose-related adverse events, especially nervous system symptoms. Efavirenz should not be used in patients with severe hepatic impairment and therefore **MYLONZA** should not be used in these patients (see 4.3).

Method of administration

Oral use.

4.3 Contraindications

- **MYLONZA** tablets are contraindicated in patients with known hypersensitivity to tenofovir, lamivudine or efavirenz, or any of the excipients.
- A history of previous liver injury/failure with efavirenz containing antiretroviral treatment.
- Severe hepatic impairment (Child-Pugh Class C)
- Moderate to severe renal impairment (CrCl < 50 mL/min). Uncontrolled renal failure.
- Pregnancy and lactation
- Concurrent administration with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, ergot alkaloids, St John’s wort (hypericum perforatum), zalcitabine or

with elbasvir/grazoprevir.

4.4 Special warnings and precautions for use

MYLONZA should not be taken with any other medicinal products containing tenofovir disoproxil fumarate, lamivudine or efavirenz.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

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

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.

Opportunistic infections

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

Lactic acidosis / hyperlactataemia

Use of **MYLONZA** can result in potentially fatal lactic acidosis as a consequence of

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

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, 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 **MYLONZA** to patients with known risk factors for liver disease. Treatment with **MYLONZA** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (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 sign and symptoms.

Pancreatitis

Pancreatitis has been observed in some patients receiving **MYLONZA**.

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

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of **MYLONZA** is increased due to decreased clearance. **MYLONZA** is not for use in patients with a CrCl of < 50 mL/min (see 4.3).

Liver disease

MYLONZA should not be used in patients with severe hepatic impairment (Child-Pugh Class C) (see 4.3).

Use of **MYLONZA** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **MYLONZA** 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 discontinuation of treatment must be considered.

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

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

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue **MYLONZA** 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 **MYLONZA** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Efavirenz

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 therapy has been initiated or even stopped. Risk factors include younger age, CD4+ counts ≥ 350 cells/µ1 and female gender.

Patients on **MYLONZA** 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 **MYLONZA** or efavirenz containing medicines should be stressed. Patients who discontinued treatment with **MYLONZA** should be followed up for symptoms/signs of liver failure for up to 12 months.

MYLONZA is not recommended in patients with moderate to severe hepatic impairment because there are insufficient data to determine whether dose adjustments are required (see 4.3).

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

Rash:

Mild to moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1 % of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was 0,14 %. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus.

Rash was reported in 26 of 57 children (46 %) treated with efavirenz and was severe in three patients (5 %). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Nervous system symptoms:

Nervous system symptoms have been reported in clinical studies with efavirenz. In addition, there have been reports of psychosis-like reactions, such as delusions and inappropriate behavior (including aggressive reactions), predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both efavirenz-treated and control-treated patients,

particularly in patients with a previous history of depression. Patients should be advised that if they experience these symptoms they should contact their doctor immediately because discontinuation of efavirenz may be required.

Lactose

MYLONZA contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, total lactase deficiency, glucose-galactose malabsorption should not take **MYLONZA.**

4.5 Interaction with other medicines and other forms of interaction

Tenofovir disoproxil fumarate

Based on the results of *in vitro* experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low. Tenofovir is excreted renally, both by filtration and active secretion via the anionic transporter (hOAT1). Co-administration of tenofovir disoproxil fumarate with other medicines that are also actively secreted via the anionic transporter (e.g. cidofovir may result in increased concentrations of tenofovir or of the co-administered medicine.

Concomitant antiretroviral medicinal products:

Emtricitabine, lamivudine, indinavir, efavirenz, nelfinavir, and saquinavir (ritonavir boosted): Co-administration with tenofovir disoproxil fumarate did not result in any clinically relevant interaction. When tenofovir disoproxil fumarate was administered with lopinavir/ritonavir, no changes were observed in the pharmacokinetics of lopinavir and ritonavir. Tenofovir AUC was increased by approximately 30 % when tenofovir disoproxil fumarate was administered with lopinavir/ritonavir.

Other interactions:

Co-administration of tenofovir disoproxil fumarate, methadone, ribavirin, adefovir dipivoxil or the hormonal contraceptive norgestimate/ethinyl estradiol did not result in any

pharmacokinetic interaction. Tenofovir disoproxil fumarate must be taken with food, as food enhances the bioavailability of tenofovir. Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

Lamivudine

Interaction studies have only been performed in adults. An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully assessed. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine. Co-administration of lamivudine with intravenous ganciclovir or foscarnet is not recommended. The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance. Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of *Pneumocystis 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) are eliminated only in part by this

mechanism and were shown not to interact with lamivudine. The nucleoside analogues (e.g. didanosine and zalcitabine) like zidovudine are not eliminated by this mechanism and are unlikely 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. Lamivudine metabolism does not involve CYP3A, making interactions with medicines metabolised by this system (e.g. PIs) unlikely.

Efavirenz

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP isozymes including CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicines or food (for example, grapefruit juice) which affect CYP3A4 activity.

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example ergotamine, dihydroergotamine, ergonovine, and methylergonovine) since inhibition of their metabolism may lead to serious, life-threatening events.

Concomitant antiretroviral medicines

Protease Inhibitors

Amprenavir:

No dosage adjustment is necessary if efavirenz is given in combination with amprenavir (600 mg twice daily) and ritonavir (100 or 200 mg twice daily).

Further, if efavirenz is given in combination with amprenavir and nelfinavir, no dosage adjustment is necessary for any of the medicinal products. Treatment with efavirenz in combination with amprenavir and saquinavir is not recommended, as the exposure to both PIs

is expected to be significantly decreased. No dose recommendation can be given for the co administration of amprenavir with another PI and efavirenz in children and patients with renal impairment. Such combinations should be avoided in patients with hepatic impairment.

Atazanavir:

Co-administration of efavirenz and atazanavir in combination with ritonavir may lead to increases in efavirenz exposure which may worsen the tolerability profile of efavirenz. Co-administration of efavirenz 600 mg with atazanavir in combination with low-dose ritonavir resulted in substantial decreases in atazanavir exposure, necessitating dosage adjustment of atazanavir.

Indinavir:

No adjustment of the dose of efavirenz is necessary when given with indinavir or indinavir/ritonavir.

Lopinavir/ritonavir:

When co‑administered with efavirenz, an increase of the lopinavir/ritonavir doses by 33 % should be considered (4 capsules/~6,5 ml twice daily instead of 3 capsules/5 ml twice daily). Caution is warranted since this dosage adjustment might be insufficient in some patients.

Nelfinavir:

No dose adjustment is necessary when nelfinavir is administered in combination with efavirenz.

Ritonavir:

When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (for example, dizziness, nausea, paraesthesia and elevated liver enzymes

occurred).

Saquinavir:

Use of efavirenz in combination with saquinavir as the sole PI is not recommended.

Saquinavir/ritonavir:

No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir.

NRTIs:

Clinically significant interactions would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

NNRTIs:

No studies have been performed with efavirenz in combination with other NNRTIs and the potential for pharmacokinetic or pharmacodynamic interactions is unknown.

Antimicrobial medicines:

Rifamycins: Rifampicin reduced efavirenz AUC by 26 % and C_{max} by 20 % in uninfected volunteers. The dose of efavirenz must be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with efavirenz. In one study in uninfected volunteers, efavirenz induced a reduction in rifabutin C_{max} and AUC by 32 % and 38 % respectively. Rifabutin had no significant effect on the pharmacokinetics of efavirenz. These data suggest that the daily dose of rifabutin should be increased by 50 % when administered with efavirenz and that the rifabutin dose may be doubled for regimens in which rifabutin is given two or three times a week in combination with efavirenz.

Macrolide antibiotics:

Azithromycin:

No dosage adjustment is necessary when azithromycin is given in combination with efavirenz.

Clarithromycin:

No dose adjustment of efavirenz is recommended when given with clarithromycin.

Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.

Antifungal medicines:

Voriconazole:

Co-administration of efavirenz and voriconazole is contraindicated.

Itraconazole:

Co-administration of efavirenz (600 mg orally once daily) with itraconazole (200 mg orally every 12 hours) in uninfected volunteers decreased the steady state AUC, C_{max}, and C_{min} of itraconazole by 39 %, 37 %, and 44 %, respectively, and of hydroxyitraconazole by 37 %, 35 %, and 43 %, respectively, compared to itraconazole administered alone. The pharmacokinetics of efavirenz were not affected. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

Other antifungal medicines:

No clinically significant pharmacokinetic interactions were seen when fluconazole and efavirenz were co-administered to uninfected volunteers. The potential for interactions with efavirenz and other imidazole and triazole antifungals, such as itraconazole and

ketoconazole, has not been studied.

Anticonvulsants:

Carbamazepine:

Co-administration of efavirenz (600 mg orally once daily) with carbamazepine (400 mg once daily) in uninfected volunteers resulted in a two-way interaction. The steady-state AUC, C_{max} and C_{min} of carbamazepine decreased by 27 %, 20 % and 35 %, respectively, while the steady-state AUC, C_{max} and C_{min} of efavirenz decreased by 36 %, 21 %, and 47 %, respectively. The steady-state AUC, C_{max} and C_{min} of the active carbamazepine epoxide metabolite remained unchanged. Carbamazepine plasma levels should be monitored periodically. There are no data with co-administration of higher doses of either medicinal product; therefore, no dose recommendation can be made, and alternative anticonvulsant treatment should be considered.

Other anticonvulsants:

No data are available on the potential interactions of efavirenz with phenytoin, phenobarbitone, or other anticonvulsants that are substrates of CYP450 isozymes. When efavirenz is administered concomitantly with these medicines, there is a potential for reduction or increase in the plasma concentrations of each medicine; therefore, periodic monitoring of plasma levels should be conducted. Specific interaction studies have not been performed with efavirenz and vigabatrin or gabapentin. Clinically significant interactions would not be expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and would be unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.

Lipid-lowering medicines:

Co-administration of efavirenz with the HMG-CoA reductase inhibitors atorvastatin,

pravastatin, or simvastatin has been shown to reduce the plasma concentration of the statin in uninfected volunteers. Cholesterol levels should be periodically monitored. Dosage adjustments of statins may be required.

Other interactions:

Antacids/famotidine:

Neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz in uninfected volunteers. These data suggest that alteration of gastric pH by other medicinal products would not be expected to affect efavirenz absorption.

Oral contraceptives:

Only the ethinylestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinylestradiol was increased (37 %) after multiple dosing of efavirenz. No significant changes were observed in C_{max} of ethinylestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinylestradiol on efavirenz C_{max} or AUC was observed. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

Methadone:

In a study of HIV infected IV medicine users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The 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.

St. John's wort (*Hypericum perforatum*):

Plasma levels of efavirenz can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort. Herbal preparations containing St. John's wort must not be used concomitantly with efavirenz. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort and the dose of efavirenz may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment.

Antidepressants:

There were no clinically significant effects on pharmacokinetic parameters when paroxetine and efavirenz were co-administered. No dose adjustments are necessary for either efavirenz or paroxetine when these medicinal products are co-administered. Since fluoxetine shares a similar metabolic profile with paroxetine, i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine. Sertraline, a CYP3A4 substrate, did not significantly alter the pharmacokinetics of efavirenz. Efavirenz decreased sertraline C_{max}, C_{24} and AUC by 28,6 to 46,3 %. Sertraline dose increases should be guided by clinical response.

Cetirizine:

No dose adjustments are necessary for either efavirenz or cetirizine when these medicinal products are co-administered.

Lorazepam:

Efavirenz increased lorazepam C_{max} and AUC by 16,3 % and 7,3 % respectively. These changes are not considered to be clinically significant. No dose adjustments are necessary.

Calcium channel blockers:

No dosage adjustment is necessary for efavirenz when administered with diltiazem.

No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme (e.g. verapamil, felodipine, nifedipine, nicardipine). When efavirenz is administered concomitantly with one of these medicines, there is a potential for reduction in the plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker).

4.6 Fertility, pregnancy and lactation

Pregnancy

MYLONZA is contraindicated during pregnancy (see 4.3).

Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of **MYLONZA** due to the efavirenz component.

Tenofovir disoproxil fumarate

No clinical data on exposed pregnancies are available for tenofovir disoproxil fumarate. Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, foetal development, parturition or postnatal development.

However, given that the potential risks to developing human foetuses are unknown, the use of tenofovir disoproxil fumarate is not recommended in women of childbearing potential.

Lamivudine

The safety of lamivudine in human pregnancy has not been established. Reproductive studies in animals have not shown evidence of teratogenicity and showed no effect on male or female fertility. Lamivudine induces early embryonic death when administered to pregnant

rabbits at exposure levels comparable to those achieved in man. In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

Efavirenz

Pregnancy should be avoided in women treated with efavirenz. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. Efavirenz should not be used during pregnancy.

There are no adequate and well-controlled studies of efavirenz in pregnant women. In post marketing experience through an antiretroviral pregnancy registry, more than 200 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. Retrospectively in this registry, a small number of cases of neural tube defects, including meningomyelocele, have been reported but causality has not been established. Studies in animals have shown reproductive toxicity including marked teratogenic effects.

Breastfeeding

MYLONZA is contraindicated during breastfeeding (see 4.3).

Tenofovir disoproxil fumarate

In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Therefore, it is recommended that mothers being treated with tenofovir disoproxil fumarate do not breast-feed their infants. As a general rule, it is recommended that HIV infected women do not breast-feed their infants in order to avoid transmission of HIV to the infant.

Lamivudine

Following oral administration lamivudine was excreted in breast milk at similar concentrations to those found in serum. Since lamivudine and the virus pass into breast milk, it is recommended that mothers taking Lamivudine Tablets do not breast-feed their infants. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Efavirenz

Studies in rats have demonstrated that efavirenz is excreted in milk reaching concentrations much higher than those in maternal plasma. It is not known whether efavirenz is excreted in human milk. Since animal data suggest that the substance may be passed into breast milk, it is recommended that mothers taking efavirenz do not breast feed their infants. It is recommended that HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate. Efavirenz may cause dizziness, impaired concentration, and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Tenofovir disoproxil fumarate

Assessment of adverse reactions is based on post-marketing experience and experience in two studies in 653 treatment-experienced patients receiving treatment with tenofovir disoproxil fumarate (n = 443) or placebo (n = 210) in combination with other antiretroviral medicinal products for 24 weeks and also in a double-blind comparative controlled study in which 600

treatment-naïve patients received treatment with tenofovir disoproxil 245 mg (as fumarate) (n = 299) or stavudine (n = 301) in combination with lamivudine and efavirenz for 144 weeks.

Approximately one third of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil fumarate in combination with other antiretroviral agents. These reactions are usually mild to moderate gastrointestinal events.

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and absolute frequency.

Metabolism and nutrition disorders:

Frequent: hypophosphataemia

Less frequent: lactic acidosis

Nervous system disorders:

Frequent: dizziness

Respiratory, thoracic and mediastinal disorders:

Less frequent: dyspnoea

Gastrointestinal disorders:

Frequent: diarrhoea, nausea, vomiting, flatulence

Less frequent: pancreatitis

Hepatobiliary disorders:

Less frequent: increased transaminases, hepatitis

Skin and subcutaneous tissue disorders:

Less frequent: rash

Musculoskeletal and connective tissue disorders:

Frequency not known: myopathy, osteomalacia (both associated with proximal renal tubulopathy)

Renal and urinary disorders:

Less frequent: renal failure, acute renal failure, proximal tubulopathy (including Fanconi syndrome), increased creatinine, acute tubular necrosis

Frequency not known: nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.

General disorders and administration site conditions:

Less frequent: asthenia

Approximately 1 % of tenofovir disoproxil fumarate treated patients discontinued treatment due to the gastrointestinal events.

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

Combination antiretroviral therapy has been associated with 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).

In a 144-week controlled clinical study in antiretroviral-naïve patients that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz, patients who received tenofovir disoproxil had a significantly lower incidence of lipodystrophy compared with patients who received stavudine. The tenofovir disoproxil fumarate arm also had significantly smaller mean increases in fasting triglycerides and total cholesterol than the comparator arm.

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.

Lamivudine

The following adverse reactions have been reported during therapy for HIV disease with lamivudine.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency.

Blood and lymphatic systems disorders

Less frequent: Neutropenia and 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 pain or 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.

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 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 of which is unknown.

Efavirenz

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below.

Immune system disorders

Less frequent: Hypersensitivity

Frequency unknown: Immuno-allergic liver injury/failure

Psychiatric disorders

Frequent: Anxiety, depression

Less frequent: Affect lability, aggression, euphoric mood, hallucination, mania, paranoia, suicide attempt, suicide ideation

Nervous system disorders

Frequent: Abnormal dreams, disturbance in attention, dizziness, headache, insomnia, somnolence

Less frequent: Agitation, amnesia, ataxia, abnormal coordination, confusional state, convulsions, abnormal thinking

Eye disorders

Less frequent: Blurred vision

Ear and labyrinth disorders

Less frequent: Vertigo

Gastrointestinal disorders

Frequent: Abdominal pain, diarrhoea, nausea, vomiting

Less frequent: Acute pancreatitis

Hepatobiliary disorders

Less frequent: Acute hepatitis

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritus

Less frequent: Erythema multiforme

General disorders and administration site conditions

Frequent: Fatigue

Reproductive system and breast disorders

Less frequent: Gynaecomastia

Immune Reactivation Syndrome

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.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with 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.

Osteonecrosis

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

Laboratory test abnormalities

Liver enzymes

Elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) to greater than five times the upper limit of the normal range (ULN) were seen in 3 % of 1,008 patients treated with 600 mg of efavirenz (5 - 8 % after long-term treatment in study 006). Similar elevations were seen in patients treated with control regimens (5 % after long-term treatment). Elevations of gamma-glutamyltransferase (GGT) to greater than five times ULN

were observed in 4 % of all patients treated with 600 mg of efavirenz and 1,5 - 2 % of patients treated with control regimens (7 % of efavirenz-treated patients and 3 % of control-treated patients after long-term treatment). Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction. In the long-term study (006), 1 % of patients in each treatment arm discontinued because of liver or biliary system disorders.

In the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, elevations in AST to greater than five times ULN developed in 13 % of patients in the efavirenz arms and 7 % of those in the control arm, and elevations in ALT to greater than five times ULN developed in 20 % of patients in the efavirenz arms and 7 % of the patients in the control arm. Among co-infected patients, 3 % of those treated with efavirenz-containing regimens and 2 % in the control arm discontinued from the study because of liver or biliary system disorders. Reasons for discontinuation among co-infected recipients of efavirenz included abnormalities in hepatic enzymes; there were no discontinuations reported in this study for cholestatic hepatitis, hepatic failure, or fatty liver.

Amylase

In the clinical trial subset of 1,008 patients, asymptomatic increases in serum amylase levels greater than 1,5 times the upper limit of normal were seen in 10 % of patients treated with efavirenz and 6 % of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown.

Lipids

Increases in total cholesterol of 10 - 20 % have been observed in some uninfected volunteers

receiving efavirenz. In clinical trials of various efavirenz-containing regimens in treatment naive patients, total cholesterol, HDL-cholesterol, and triglycerides increased over 48 weeks of treatment (21 - 31 %, 23 - 34 %, and 23 - 49 %, respectively). The proportion of patients with a total cholesterol/HDL-cholesterol ratio greater than 5 was unchanged. The magnitude of changes in lipid levels may be influenced by factors such as duration of therapy and other components of the antiretroviral regimen.

Cannabinoid test interaction

Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz. False positive test results have only been observed with the CEDIA DAU Multi Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

Post marketing experience with efavirenz has shown the following additional adverse events to occur in association with efavirenz-containing antiretroviral treatment regimens: delusion, gynaecomastia, hepatic failure, neurosis, photoallergic dermatitis, psychosis and completed suicide.

4.9 Overdose

Tenofovir disoproxil fumarate

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

Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. The elimination of tenofovir by peritoneal dialysis has not been studied.

Lamivudine

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.
If overdosage occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, although this has not been studied.

Efavirenz

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antivirals for systemic use, ATC code J05AR11 Antivirals for treatment of HIV infections, combinations.
Pharmacological classification: A 20.2.8 Antiviral agents

Tenofovir disoproxil fumarate

Pharmacodynamic properties

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The IC_{50} (50 % inhibitory concentration) values for tenofovir were in the range of 0,04 µM to 8,5 µM. In medicine combination studies of tenofovir with nucleoside

reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (IC_{50} values ranged from 0,5 µM to 2,2 µM). The IC_{50} values of tenofovir against HIV-2 ranged from 1,6 µM to 4,9 µM.

Mechanism of action

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate and is converted *in vivo* to tenofovir. It is a nucleoside reverse transcriptase inhibitor.

Tenofovir is phosphorylated by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase, by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation in DNA, by chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, ß and mitochondrial DNA polymerase γ.

Drug resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2-4 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 agents. In treatment-naïve patients treated with tenofovir + lamivudine + efavirenz, viral isolates from 8/47 (17 %) patients with virologic failure showed reduced susceptibility to tenofovir.

In treatment-experienced patients, 14/304 (4,6 %) of the tenofovir-treated patients with virologic failure through week 96 showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene

resulting in the K65R amino acid substitution.

Cross-resistance

Cross-resistance among certain reverse transcriptase inhibitors has been recognised. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations, showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Pharmacokinetic properties

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25 %. Following oral administration of a single dose of tenofovir 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1,0 $\pm$ 0,4 hrs. C_{max} and AUC values are 296 $\pm$ 90 ng/mL and 2287 $\pm$ 685 ng*h/mL, respectively. The pharmacokinetics of tenofovir are dose proportional over a dose range of 75 to 600 mg and are not affected by repeated dosing.

Effects of food on oral absorption

Administration of tenofovir following a high fat meal increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40 % and an increase in 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 substance. 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.

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0,7 % and 7,2 %, respectively, over the tenofovir concentration range 0,01 to 25 µg/mL. The volume of distribution at steady-state is 1,3 ± 0,6 L/kg and 1,2 ± 0,4 L/kg, following intravenous administration of tenofovir 1,0 mg/kg and 3,0 mg/kg.

Metabolism and elimination

In vitro studies indicate that neither tenofovir disoproxil fumarate nor tenofovir are substrates of CYP450 enzymes. Following IV administration of tenofovir, approximately 70 - 80 % of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir 300 mg once daily (under fed conditions), 32 ± 10 % of the administered dose is recovered in urine over 24 hours. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special populations

Paediatrics and the elderly

There were insufficient numbers from racial and ethnic groups, other than Caucasian, to

adequately determine potential pharmacokinetic differences among these populations. Tenofovir pharmacokinetics are similar in male and female patients. Pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (> 65 years).

Hepatic impairment

Tenofovir pharmacokinetics after a 300 mg single dose 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. Change in tenofovir dosing is not required in patients with hepatic impairment.

Renal impairment

Tenofovir pharmacokinetics are altered in patients with renal impairment. In patients with creatinine clearance < 50 mL/min or with end stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased (Table 1). It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see Section 4.2).

Table 1 Pharmacokinetic parameters (Mean ± SD) of tenofovir in patients with varying degrees of renal function

Baseline creatinine clearance (mL/min)	**>80 (N=3)**	**50-80 (N=10)**	**30-49 (N=8)**	**12-28 (N=11)**
C_{max} (ng/mL)	335,4 ± 31,8	330,4 ± 61,0	372,1 ± 156,1	601,6 ± 185,3
$AUC_{0-\infty}$ ng*hr/mL	2184,5 ± 257,4	3063,8 ± 927,0	6008,5 ± 2504,7	15984,7 ± 7223,0
CL/F mL/min	1043,7 ± 115,4	807,7 ± 279,2	444,4 ± 209,8	177,0 ± 97,1
CL_{renal} mL/min	243,5 ± 33,3	168,6 ± 27,5	100,6 ± 27,5	43,0 ± 31,2

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

Lamivudine

Pharmacodynamic properties

Lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI), is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro*. It is also active against zidovudine-resistant clinical isolates of human immunodeficiency virus (HIV).

Lamivudine is metabolised intracellularly to the 5'-triphosphate which has an intracellular half-life of 16 – 19 hours. Lamivudine 5'-triphosphate is a weak inhibitor of the RNA and DNA dependent activities of HIV reverse transcriptase, its mode of action is a chain terminator of HIV reverse transcription.

Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture.

Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content.

In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells.

Lamivudine-resistant variants of HIV-1 have been selected *in vitro*. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either isoleucine or valine. HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients.

Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harbouring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine.

Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine. Lamivudine-resistant HIV-1 mutants were cross resistant to didanosine and zalcitabine. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged. Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolates from patients who have received lamivudine therapy. Evidence from clinical studies show that lamivudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy.

The relationship between *in vitro* susceptibility of HIV to lamivudine and the clinical response to therapy remain under investigation.

Pharmacokinetic properties

Pharmacokinetics in adults

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 to 85 %. Following oral administration, the mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels i.e. 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1-1,5 µg/mL. From intravenous studies, the mean volume of distribution is 1,3 L/kg and the mean terminal half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 L/kg/h, with predominantly renal clearance (>70 %) via active tubular secretion, but little (< 10 %) hepatic metabolism. No dose adjustment is needed when co-administered with food

as lamivudine bioavailability is not altered, although a delay in T_{max} and reduction in C_{max} have been observed. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin. Lamivudine elimination will be affected by renal impairment, whether it is disease or age related. A recommended dosage regimen for patients with creatinine clearance below 50 mL/min is shown in the dosage section. Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary. The likelihood of adverse drug interactions with lamivudine is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the lamivudine/zidovudine combination in patients with renal impairment should be carefully assessed.

Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Pharmacokinetics in children

Lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability (approximately 55-65 %) was reduced in paediatric patients below 12 years of age. In addition, systemic clearance values were greater in younger paediatric patients and decreased with age approaching adult values around 12 years of age. Recent findings

indicate that exposure in children 2 to < 6 years of age may be reduced by about 30 % compared with other age groups. At present, the available data do not suggest that lamivudine is less efficacious in this group. There are limited pharmacokinetic data for patients <3 months of age. In neonates one week of age, lamivudine oral clearance was reduced when compared to paediatric patients and is likely due to immature renal function and variable absorption.

Pharmacokinetics in pregnancy

Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant adults. Administration of lamivudine in animal toxicity studies at very high doses was not associated with any major organ toxicity. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia. Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity of an *in vitro* cytogenic assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 30–40 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed *in vivo* tests it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment. There is a yet no information on the tumorigenic risk in animals, and therefore any potential risk to man must be balanced against the expected benefits of treatment.

Efavirenz

Pharmacodynamic properties

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts < 50 cells/mm^3, or in PI or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited.

Mechanism of action

Efavirenz is a NNRTI of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases (α, β, γ or δ).

Antiviral activity

The free concentration of efavirenz required for 90 to 95 % inhibition of wild type or zidovudine resistant laboratory and clinical isolates *in vitro* ranged from 0,46 to 6,8 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures.

Resistance

The potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine-to-isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine-to-asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT. K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. This mutation was observed in 90 % of patients receiving efavirenz with virological failure. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medications used in combination with efavirenz.

Cross resistance

Cross resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine-resistant clinical isolates examined were cross resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross-resistant to efavirenz. Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical studies who showed evidence of treatment failure (viral load rebound) were assessed for susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz-resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI-resistant isolates were found to have K103N or a valine-to-isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine. The potential for cross resistance between efavirenz and PIs is low because of the different enzyme targets involved. The potential for cross resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action.

Pharmacokinetic properties

Absorption

Peak efavirenz plasma concentrations of 1,6 to 9,1 µM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers. Dose related increases in C_{max} and AUC were seen for doses up to 1,600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3-5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6-7 days. In HIV infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady state C_{max} was 12,9 ± 3,7 µM (29 %)

[Mean ± S.D. (% C.V.)], steady state C_{min} was 5,6 ± 3,2 µM (57 %), and AUC was 184 ± 73 µM·h (40 %).

Effect of food

The AUC and C_{max} of a single 600 mg dose of efavirenz film coated tablets in uninfected volunteers was increased by 28 % (90 % CI: 22-33 %) and 79 % (90 % CI: 58-102 %), respectively, when given with a high fat meal, relative to when given under fasted conditions.

Distribution

Efavirenz is highly bound (approximately 99,5-99,75 %) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n = 9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0,26 to 1,19 % (mean 0,69 %) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Biotransformation

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. In *in vitro* studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. In uninfected volunteers, multiple doses of 200-400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 - 42 % lower) and a shorter

terminal half-life of 40-55 hours (single dose half-life 52-76 hours).

Elimination

Efavirenz has a relatively long terminal half-life of 52 to 76 hours after single doses and 40-55 hours after multiple doses. Approximately 14-34 % of a radiolabelled dose of efavirenz was recovered in the urine and less than 1 % of the dose was excreted in urine as unchanged efavirenz.

Hepatic impairment

In the single patient studied with severe hepatic impairment (Child Pugh Grade C), half-life was doubled indicating a potential for a much greater degree of accumulation.

Gender, race, elderly

Although limited data suggest that Asian and Pacific Island patients may have higher exposure to efavirenz, they do not appear to be less tolerant of efavirenz. Pharmacokinetic studies have not been performed in the elderly.

Paediatric use

MYLONZA has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg. In a clinical trial of 57 paediatric patients, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of new-onset rash in children (46 %). The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Microcrystalline cellulose, croscarmellose sodium, ferric oxide, hydroxypropyl cellulose,

lactose monohydrate, magnesium stearate, sodium lauryl sulfate. Film coat: Opadry II White {macrogol, polyvinyl alcohol, talc, titanium dioxide}.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original container. Do not remove from the carton until required for use. Keep the bottles tightly closed.

6.5 Nature and contents of container

Round, wide mouth, white, high density polyethylene (HDPE) bottle with white opaque polypropylene cap along with desiccant. Pack size: 30 tablets.

Blue high-density polyethylene (HDPE) bottle with blue opaque polypropylene cap along with desiccant. Pack size: 30 tablets.

The HDPE bottle may be placed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

1600

Republic of South Africa

8 REGISTRATION NUMBER

MYLONZA: 54/20.2.8/0052.051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 03/05/2022

10 DATE OF REVISION OF THE TEXT

03/05/2022