Module 1.3.1.1: PACKAGE INSERT FOR

MIVUTEN TABLETS

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

MIVUTEN (Tablets)

COMPOSITION:

Each film-coated tablet contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate, equivalent to 245 mg of tenofovir disoproxil. The inactive ingredients include corn starch, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and polysorbate 80.

Contains lactose.

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 "WARNINGS"). EARLY SYMPTOMS (SYMPTOMATIC HYPERLACTATAEMIA) INCLUDE BENIGN DIGESTIVE SYMPTOMS (NAUSEA, VOMITING AND ABDOMINAL PAIN), NON-SPECIFIC MALAISE, LOSS OF APPETITE, WEIGHT LOSS, RESPIRATORY SYMPTOMS (RAPID AND/OR DEEP BREATHING) OR NEUROLOGICAL SYMPTOMS (INCLUDING MOTOR

WEAKNESS). LACTIC ACIDOSIS HAS A HIGH MORTALITY AND MAY BE ASSOCIATED WITH PANCREATITIS, LIVER FAILURE OR RENAL FAILURE. LACTIC ACIDOSIS GENERALLY OCCURRED AFTER A FEW OR SEVERAL MONTHS OF TREATMENT.

TREATMENT WITH MIVUTEN SHOULD BE DISCONTINUED IN THE SETTING OF SYMPTOMATIC HYPERLACTATAEMIA AND METABOLIC/LACTIC ACIDOSIS, PROGRESSIVE HEPATOMEGALY, OR RAPIDLY ELEVATING AMINOTRANSFERASE LEVELS.

CAUTION SHOULD BE EXERCISED WHEN ADMINISTERING MIVUTEN TO ANY PATIENT (PARTICULARLY OBESE WOMEN) WITH HEPATOMEGALY, HEPATITIS OR OTHER KNOWN RISK FACTORS FOR LIVER DISEASE AND HEPATIC STEATOSIS (INCLUDING CERTAIN MEDICINES AND ALCOHOL). PATIENTS CO-INFECTED WITH HEPATITIS C AND TREATED WITH ALPHA-INTERFERON AND RIBAVIRIN MAY CONSTITUTE A SPECIAL RISK.

PATIENTS AT INCREASED RISK SHOULD BE FOLLOWED CLOSELY.

MIVUTEN IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF MIVUTEN 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 MIVUTEN. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE MIVUTEN AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE,

INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE "WARNINGS").

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Lamivudine:

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

Lamivudine is metabolised intracellularly to the active 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.

Resistance:

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.

Cross-resistance:

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 plus zidovudine 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.

Tenofovir disoproxil fumarate:

Tenofovir disoproxil fumarate 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 reverse transcriptase by competing with the natural substance 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.

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocytes, macrophage cells and peripheral blood lymphocytes. The IC_{50} values for tenofovir are 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.

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- to 4-fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral agents.

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 medicines may occur in patients whose virus harbours the K65R mutation. HIV-1 isolates from patients whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), showed a 3,1-fold decrease in susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Pharmacokinetics:

Lamivudine:

Absorption:

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 of 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1 – 1,5 µg/mℓ.

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.

Distribution:

The mean volume of distribution is 1,3 ℓ/kg and the mean terminal half-life of elimination as 5 to 7 hours.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin.

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 is approximately 0,12. The true extent of penetration or relationship with any clinical efficacy is unknown.

Metabolism and elimination:

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.

Tenofovir disoproxil fumarate:

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 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 disoproxil fumarate 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1,0 ± 0,4 hours. C_{max} and AUC values are 296 ± 90 ng/mℓ and 2287 ± 685 ng*h/mℓ, respectively.

The pharmacokinetics of tenofovir are dose proportional and independent of tenofovir disoproxil fumarate dose over the dose range 75 to 600 mg and are not affected by repeated dosing.

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} by approximately 14 %. However, administration of tenofovir disoproxil fumarate with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared with fasted administration. 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 protein binding of tenofovir to plasma or serum proteins is less than 0,7 and 7,2 %, respectively, over the tenofovir concentration range of 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, respectively, following intravenous administration of tenofovir 1,0 mg/kg and 3,0 mg/kg.

Metabolism:

In vitro studies indicate that neither tenofovir disoproxil fumarate nor tenofovir are substrates of CYP450 enzymes.

Elimination:

Following intravenous 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:

Gender/age:

In general, 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. Due to these differences, the recommended dose for children from 3 months to 12 years is 8 mg/kg/day, which will provide comparable exposure to the recommended adult dose.
There are limited pharmacokinetic data for patients < 3 months of age.

Tenofovir pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (> 65 years).

Renal impairment:
The pharmacokinetics of tenofovir 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 of tenofovir are increased. It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance < 50 mℓ/min or with ESRD requiring dialysis. Since this is not possible with a fixed dose combination, use of appropriate formulations of the individual preparations is recommended (see **"CONTRA-INDICATIONS"** and **"WARNINGS"**).

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 elimination will be affected by renal impairment, whether it is disease- or age-related (see **"CONTRA-INDICATIONS"**).

Hepatic impairment:

There are no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in tenofovir dosing is required in patients with hepatic impairment.

INDICATIONS:

MIVUTEN is indicated in combination with other antiretroviral medicines for the treatment of HIV infected adults over 18 years of age.

CONTRA-INDICATIONS:

MIVUTEN is contra-indicated in:

- Patients with hypersensitivity to lamivudine or tenofovir or to any of the components of **MIVUTEN**.
- Patients with moderate to severe renal impairment (CrCl less than 50 mℓ/min) (see **"Pharmacokinetics"**), since dose adjustments are not possible with a fixed dose combination such as **MIVUTEN**.
- Pregnancy and lactation (see **"PREGNANCY AND LACTATION"**).
- Patients younger than 18 years of age.
- Concomitant use with zalcitabine (see **"INTERACTIONS"**).

WARNINGS:

Lactic acidosis/severe hepatomegaly with steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, as contained in **MIVUTEN** (see initial boxed **"WARNING"**). A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues, as contained in **MIVUTEN**, to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with **MIVUTEN** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence or marked transaminase elevations) (see **"Special Precautions"**).

Renal disease:

See **"CONTRA-INDICATIONS"** and **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**.

The tenofovir in **MIVUTEN** is principally eliminated by the kidney. Dosing interval adjustment is recommend in all patients with creatinine clearance < 50 mℓ/min. Also, in patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance and dosage adjustment is therefore required. Since this is not possible with a fixed dose combination such as **MIVUTEN**, use of appropriate formulations of the individual preparations are recommended (see **"CONTRA-INDICATIONS"**).

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) has been reported in association with the use of tenofovir, as contained in **MIVUTEN** (see **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**).

MIVUTEN should be avoided with concurrent use of a nephrotoxic agent. Patients at risk of, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

Patients with HIV and hepatitis B virus co-infection:

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy (see initial boxed **"WARNING"**). **MIVUTEN** is not indicated for the treatment of chronic HBV infection and the safety and efficacy of **MIVUTEN** have not been established in patients co-infected with HBV and HIV. Severe, acute exacerbations of HBV have been reported in patients after the discontinuation of the tenofovir in **MIVUTEN**. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping tenofovir treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Fat redistribution:

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, "cushingoid appearance", and elevated serum lipid and glucose levels have been observed either separately or together in some patients receiving combination

antiretroviral therapy, such as **MIVUTEN** (see **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**).

The lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral therapy all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

INTERACTIONS:

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

The likelihood of adverse medicine interactions with the lamivudine in **MIVUTEN** is low due to the limited metabolism and plasma protein binding and almost complete renal clearance.

At concentrations substantially higher (~ 300-fold) than those observed *in vivo*, tenofovir did not inhibit *in vitro* medicine metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9 or CYP2E1. However, a small (6 %) but statistically significant reduction in metabolism of CYP1A substrate was observed. 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, as contained in **MIVUTEN**, is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of **MIVUTEN** with medicines that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or of the co-administered medicine, due to competition for this elimination pathway. Medicines that decrease renal function may also increase serum concentrations of the tenofovir in **MIVUTEN**.

Abacavir:

There have been reports of a high rate of virological failure and of emergence of resistance at early stage when tenofovir disoproxil fumarate and lamivudine, as contained in **MIVUTEN**, was combined with abacavir as a once-daily regimen.

Adefovir dipivoxil:

MIVUTEN should not be co-administered with adefovir dipivoxil.

Atazanavir:

The tenofovir in **MIVUTEN** decreases the AUC and C_{min} of atazanavir by 25 % and 40 %, respectively. The negative impact of tenofovir on atazanavir C_{min} is significantly reduced, whereas the decrease in AUC is of the same magnitude (decrease of 25 % and 26 % of AUC and C_{min}, respectively compared to atazanavir/ritonavir 300/100 mg) when ritonavir is added to atazanavir. Co-administration of atazanavir/ritonavir with tenofovir, as contained in **MIVUTEN**, results in increased exposure to tenofovir. Higher tenofovir concentrations could

potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored.

Didanosine:

Co-administration of **MIVUTEN** is not recommended. Co-administration of tenofovir, as contained in **MIVUTEN**, and didanosine results in a 40 – 60 % increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse events. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.

Darunavir/ritonavir:

Co-administration of tenofovir, as contained in **MIVUTEN**, once daily with darunavir/ritonavir 300/100 mg twice daily had no significant effect on darunavir/ritonavir pharmacokinetic parameters. Tenofovir AUC is increased by approximately 22 % and tenofovir C_{min} with 37 %. No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored.

Efavirenz:

Concomitant administration of efavirenz 600 mg once daily for 14 days with tenofovir 300 mg, as in **MIVUTEN**, once daily did not result in any changes in the $C_{max,}$ C_{min} or AUC of either efavirenz or tenofovir.

Emtricitabine:

Co-administration of emtricitabine 200 mg once daily for 7 days with tenofovir 300 mg, as in **MIVUTEN**, once daily did not result in any changes in the C_{max}, C_{min} or AUC of tenofovir. While the C_{max}, and AUC of emtricitabine were unchanged, the C_{min} increased by 20 % (90 % CI + 12 % to + 29 %).

Indinavir:

There was a 14 % increase (90 % CI - 3 % to + 33 %) in the C_{max} of tenofovir when indinavir 800 mg three times daily for 7 days was co-administered with tenofovir 300 mg, as in **MIVUTEN**, once daily. The C_{min} and AUC of tenofovir remained unchanged as did the C_{min} and AUC of indinavir. Indinavir C_{max} decreased by 11 % (90 % CI - 30 % to + 12 %).

Lopinavir/ritonavir:

Co-administration of tenofovir, as contained in **MIVUTEN**, and lopinavir/ritonavir does not result in changes in the pharmacokinetics of lopinavir and ritonavir. Tenofovir AUC is increased by approximately 30 % when tenofovir is administered with lopinavir/ritonavir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Renal function should be closely monitored.

Trimethoprim:

An interaction between the lamivudine in **MIVUTEN** and trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine plasma concentrations at therapeutic doses. This does not require dosage adjustment of the lamivudine in **MIVUTEN**, unless the patient also has renal impairment. The lamivudine in **MIVUTEN** has no effect on the pharmacokinetics of co-trimoxazole.

Zalcitabine:

The lamivudine in **MIVUTEN** may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. **MIVUTEN** is therefore not recommended to be used in combination with zalcitabine (see **"CONTRA-INDICATIONS"**).

Zidovudine:

Zidovudine plasma levels are not significantly altered when co-administered with the lamivudine in **MIVUTEN**. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Other:

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

Specifically, when methadone 40 – 110 mg once daily for 14 days was co-administered with tenofovir 300 mg, as in **MIVUTEN**, once daily, R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

Use of **MIVUTEN** should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see **"WARNINGS"**). Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2.

Given that tacrolimus can affect renal function, close monitoring is recommended when it is co-administered with the tenofovir in **MIVUTEN**.

PREGNANCY AND LACTATION:

Pregnancy:

The effects of **MIVUTEN** in pregnancy have not been established. **MIVUTEN** should therefore not be used during pregnancy (see **"CONTRA-INDICATIONS"**).

The use of **MIVUTEN** in women of childbearing potential must be accompanied by the use of effective contraception.

Lactation:

It is recommended that mothers being treated with **MIVUTEN** do not breastfeed their infants (see **"CONTRA-INDICATIONS"**).

It is also recommended that HIV infected women do not breastfeed their infants in order to avoid transmission of HIV to the infant.

DOSAGE AND DIRECTIONS FOR USE:

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

Adults and adolescents older than 18 years:

The recommended dose of **MIVUTEN** is one tablet once daily taken orally with food.

Paediatric patients:

MIVUTEN is not recommended for use in children below the age of 18 years.

Elderly:

Caution should be taken when treating patients older than 65 years with **MIVUTEN** (see **"Special Precautions"**).

Renal impairment:

MIVUTEN should not be used in patients with moderate to severe renal impairment (see **"CONTRA-INDICATIONS"**).

Hepatic impairment:

No dose adjustment is required in patients with hepatic impairment.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

Lamivudine:

Immune system disorders:

Less frequent: Angioedema.

Blood and lymphatic system disorders:

Less frequent: Anaemia, neutropenia, thrombocytopenia, pure red cell aplasia.

Metabolism and nutrition disorders:

Frequent: Hyperlactataemia.

Less frequent: Lactic acidosis (see **"WARNINGS"**), lipodystrophy (redistribution/accumulation of body fat) (see **"WARNINGS"**).

Nervous system disorders:

Frequent: Headache, insomnia.

Less frequent: Paraesthesia, peripheral neuropathy.

Respiratory, thoracic and mediastinal disorders:

Frequent: Cough, nasal symptoms.

Gastrointestinal disorders:

Frequent:	Nausea, vomiting, abdominal pain or cramps, diarrhoea.
Less frequent:	Pancreatitis, rises in serum amylase.

Hepato-biliary disorders:

Less frequent:	Transient rises in liver enzymes (AST, ALT), hepatitis.

Skin and subcutaneous tissue disorders:

Frequent:	Rash, alopecia.

Musculoskeletal, connective tissue and bone disorders:

Frequent:	Arthralgia, muscle disorders.
Less frequent:	Rhabdomyolysis.

General disorders:

Frequent:	Fatigue, malaise, fever.

<u>Tenofovir disoproxil fumarate:</u>

Infections and infestations:

Frequent:	Pneumonia.

Immune system disorders:

Less frequent:	Angioedema.

Frequency unknown:	Allergic reaction.

Metabolism and nutrition disorders:

Frequent:	Lipodystrophy, weight loss.
Less frequent:	Lactic acidosis.
Frequency unknown:	Hypophosphataemia.

Nervous system disorders:

Frequent:	Headache, insomnia, dizziness, peripheral neuropathy (including peripheral neuritis and neuropathy), anorexia.

Psychiatric disorders:

Frequent:	Anxiety, depression.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown:	Dyspnoea.

Gastrointestinal disorders:

Frequent:	Abdominal pain, diarrhoea, nausea, dyspepsia, vomiting, flatulence, abdominal distension.
Less frequent:	Pancreatitis.

Hepato-biliary disorders:

Frequent:	Increased transaminases.

Less frequent:	Hepatitis, hepatic steatosis.
Frequency unknown:	Increased liver enzymes.

Skin and subcutaneous tissue disorders:

Frequent:	Rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, sweating.

Musculoskeletal, connective tissue and bone disorders:

Frequent:	Arthralgia, myalgia.
Less frequent:	Rhabdomyolysis, muscular weakness, osteomalacia, and myopathy as a consequence of proximal renal tubulopathy.

Renal and urinary disorders:

Less frequent:	Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, proteinuria, increased creatinine, acute tubular necrosis, nephrogenic diabetes insipidus, nephritis (including acute interstitial nephritis).

General disorders:

Frequent:	Pain, fever, back pain, asthenia, chest pain, fatigue.

Investigations:

Frequent:	Increases in total cholesterol, raised creatine kinase, raised serum amylase, elevations in AST and ALT, haematuria, raised neutrophil count, raised triglyceride level, glycosuria, raised serum glucose. Hypophosphataemia as a consequence of proximal renal tubulopathy.
Less frequent:	Hypokalaemia as a consequence of proximal renal tubulopathy.

Special Precautions:

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

Pancreatitis:

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

Opportunistic infections:

Patients receiving **MIVUTEN** may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close

observation by medical practitioners experienced in the treatment of patients with associated HIV disease.

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including **MIVUTEN**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Immune reconstitution syndrome:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including **MIVUTEN**. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Bone mineral density:

Decreases in bone mineral density of the hip and spine have been associated with tenofovir-based treatment, such as with **MIVUTEN**. However, there was no increased risk of fracture or evidence for clinically relevant bone abnormalities. If bone abnormalities are suspected then appropriate consultation should be obtained.

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.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

Renal impairment:

The tenofovir in **MIVUTEN** is principally eliminated via the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see **"WARNINGS"**).

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with **MIVUTEN** and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year, and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.

MIVUTEN is contra-indicated in patients with creatinine clearance < 50 mℓ/min, including haemodialysis patients (see **"CONTRA-INDICATIONS"**).

If serum phosphate is < 1,5 mg/dℓ (0,48 mmol/ℓ) or creatinine clearance is decreased to < 50 mℓ/min in any patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations.

Liver disease:

Safety and efficacy data are very limited in liver transplant patients.

There are limited data on the safety and efficacy of the tenofovir disoproxil fumarate in **MIVUTEN** in HBV infected patients with decompensated liver disease and who have Child-Pugh-C (moderate to severe). These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

MIVUTEN should be used with caution in patients with advanced cirrhotic liver disease due to chronic hepatitis B infection as there is a risk of rebound hepatitis post-treatment.

Osteonecrosis:

Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Paediatric use:

Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.

Geriatric use:

Dose selection for the elderly patient should be cautions, keeping in mind the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other medicine therapy.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues, such as contained in **MIVUTEN**, 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 postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

Lactic acidosis/severe hepatomegaly with steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of **MIVUTEN** alone or in combination, in the treatment of HIV infection. Most cases were women (see **"WARNINGS"**).

Long-term use of **MIVUTEN** can result in potentially fatal lactic acidosis. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

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

- Lactate 2 – 5 mmol/ℓ: monitor regularly, and be alert for clinical signs.

- Lactate 5 – 10 mmol/ℓ without symptoms: monitor closely.
- Lactate 5 – 10 mmol/ℓ with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate > 10 mmol/ℓ: STOP all therapy (80 % mortality in case studies).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and a raised lactate level. Therapy should be stopped in any acidotic patient with a raised lactate level.

Blood for lactate assays should be heparinised and stored on ice.

After recovery, NRTI's should be avoided. Seek expert advice on medicine selection.

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

Lactose:

MIVUTEN contains lactose. **MIVUTEN** should not be administered to patients with glucose-galactose malabsorption, hereditary galactose intolerance or with the rare Lapp lactase deficiency.

Effects on the ability to drive and use machinery:

MIVUTEN may cause dizziness; patients should be advised to refrain from driving a car or operating machinery until they know how **MIVUTEN** affects them.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Tenofovir, as contained in **MIVUTEN**, 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.

IDENTIFICATION:

Capsule-shaped, bilayered, biconvex, film-coated tablets with one layer orange and the other layer white in colour, "LT" debossed on one side with central break line and plain on the other side.

PRESENTATION:

White, cylindrical HDPE bottle closed with a white opaque HDPE non child resistance cap with a white opaque liner, containing 28 or 30 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep container tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

45/20.2.8/0108

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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