# PROPOSED PACKAGE INSERT- CIPLA DUOVIR TABLETS

## SCHEDULING STATUS:

S4

## PROPRIETARY NAME (and dosage form):

**CIPLA DUOVIR** (Tablets)

## COMPOSITION:

Each coated **CIPLA DUOVIR** tablet contains 150 mg lamivudine and 300 mg zidovudine.

Inactive ingredients include colloidal silicon dioxide, hydroxypropylmethyl-cellulose, magnesium stearate, microcrystalline cellulose, propylene glycol, purified talc, sodium starch glycolate and titanium dioxide.

## PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents.

## PHARMACOLOGICAL ACTION:

### Pharmacodynamics:

Zidovudine and lamivudine are both selective inhibitors (nucleoside reverse transcriptase inhibitors, or NRTIs) of human immunodeficiency virus (HIV)-1 and HIV-2. The action of lamivudine has been shown to be synergistic with zidovudine, in the inhibition of the replication of HIV in cell culture. Both medicines are metabolised sequentially by intracellular kinases to their 5'-

triphosphate (TP) forms, respectively. Zidovudine-TP and lamivudine-TP are substrates for and competitively inhibit HIV reverse transcriptase. The main antiviral activity of these two antiretrovirals is through incorporation of their monophosphate forms into the viral DNA chain, resulting in chain termination. Lamivudine-TP and zidovudine-TP display significantly less affinity for host cell DNA polymerases.

Treatment with lamivudine and zidovudine individually has resulted in HIV clinical isolates which show reduced sensitivity *in vitro* to the nucleoside analogue to which they have been exposed. On the other hand, *in vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive whilst they simultaneously acquire resistance to lamivudine. Furthermore, there is clinical evidence *in vivo* that zidovudine plus lamivudine delays the emergence of zidovudine resistance in antiretroviral naïve patients.

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

In patients receiving lamivudine monotherapy or combination therapy with lamivudine and zidovudine, HIV-1 isolates become genotypically and phenotypically 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. There has been isolation of HIV-1 strains resistant to both lamivudine and zidovudine after extended lamivudine/zidovudine treatment. There have been no reports of cross-resistance between lamivudine and zidovudine.

HIV isolates with multi-drug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for more than or up to a year with zidovudine plus didanosine or zidovudine plus zalcitabine. There was a difference in the pattern of genotypic resistant mutations with such combination therapies (Ala62 → Val, Val75 → Ile, Phe77 → Leu, Phe116 → Tyr, and Gln151 → Met) from the pattern with zidovudine monotherapy, with the 151 mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with the mutations at 62, 75, 77 and 116 results in a virus with reduced susceptibility to zidovudine, didanosine, zalcitabine, stavudine and lamivudine.

**Pharmacokinetics:**

*Absorption*: Zidovudine and lamivudine are well absorbed from the gastrointestinal tract. The bioavailability in adults of oral lamivudine and zidovudine is 80 - 85 % and 60 - 70 %, respectively. Lamivudine/zidovudine combination, as in **CIPLA DUOVIR**, was shown to be bioequivalent to lamivudine 150 mg and zidovudine 300 mg given as separate tablets, when administered to fasting subjects.

Absorption of lamivudine is delayed, but not reduced, by ingestion with food.

Binding of lamivudine to plasma protein is reported to be less than 36 %.

Because of first-pass metabolism, systemic bioavailability of zidovudine is approximately 65 %. Bioavailability in neonates up to 14 days old is approximately 89 %, and in neonates over 14 days, it decreases to approximately 61 %.

Administration of zidovudine with a high-fat meal may decrease the rate and extent of absorption.

Although no pharmacokinetic studies have been performed with crushed tablets, the administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the clinical effect if ingested immediately.

*Distribution:* Lamivudine and zidovudine, in intravenous studies, shows mean apparent volume of distribution of 1,3 and 1,6 ℓ/kg respectively.
Medicine interactions involving binding site displacement are not anticipated with **CIPLA DUOVIR.** Zidovudine and lamivudine penetrate the central nervous system and reach the cerebrospinal fluid (CSF).

*Metabolism*: Lamivudine undergoes minimal metabolism. It is predominantly cleared by the renal route as unchanged medicine. The likelihood of drug interactions with lamivudine is therefore low due to minimal hepatic metabolism (5 - 10 %) and low plasma protein binding.
The 5'-glucuronide is the major metabolite of zidovudine in both plasma and urine. This metabolite accounts for approximately 50 - 80 % of the administered dose eliminated by renal excretion. Following intravenous dosing, 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine.

*Elimination:* The half-life of elimination of lamivudine is 5 – 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 ℓ/h/kg, with predominantly renal clearance (> 70 %) via the organic cationic transport system. Lamivudine elimination is affected by renal dysfunction; lamivudine plasma concentrations are increased in patients with moderate to severe renal impairment due to decreased

clearance. AUC and $C_{max}$ increased 419 % and 140 % respectively in moderate renal impairment, and 1 344 % and 224 % respectively for end-stage renal impairment.

The mean terminal plasma half-life of zidovudine is 1,1 hours and mean systemic clearance is 1,6 ℓ/h/kg. Renal clearance of zidovudine is approximately 0,34 ℓ/h/kg, demonstrating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

Therefore, in patients with creatinine clearance less than or equal to 50 mℓ/min, lamivudine and zidovudine must be administered as separate formulations (see **"DOSAGE AND DIRECTIONS FOR USE"**).

**Pharmacokinetics of lamivudine and zidovudine in CIPLA DUOVIR when used in combination with other antiretroviral agents:**

**Zidovudine:**

Pharmacokinetic/drug interaction studies indicate that there are no clinically significant changes to zidovudine pharmacokinetics when administered concomitantly with the following antiretroviral agents:

*Nucleoside reverse transcriptase inhibitors (NRTI's)*: abacavir, didanosine and zalcitabine;

*Non-nucleoside reverse transcriptase inhibitors (NNRTI's)*: efavirenz and nevirapine; and

*Protease inhibitors*: saquinavir mesylate, ritonavir, nelfinavir, indinavir sulphate and amprenavir.

There is however a known interaction between zidovudine and stavudine (d4T) (see "**INTERACTIONS**"). These two medicines should therefore not be administered concomitantly.

**Lamivudine:**

Pharmacokinetic /drug interaction studies indicate that there are no clinically significant changes to lamivudine pharmacokinetics when administered concomitantly with the following antiretroviral agents:

*Non-nucleoside reverse transcriptase inhibitors (NNRTI's)*: efavirenz; and

*Protease inhibitors*: ritonavir, nelfinavir, indinavir sulphate and amprenavir.

**Pharmacokinetics of lamivudine and zidovudine in CIPLA DUOVIR when used in combination with tuberculostatic medicines:**

**Zidovudine:**

The concomitant use of zidovudine and rifampicin decreases the AUC of zidovudine by approximately 48 %. However, whether this is clinically significant is not known.

**Lamivudine:**

Lamivudine undergoes minimal metabolism. It is predominantly cleared by the renal route as unchanged medicine. The likelihood of metabolic drug interactions with, e.g. rifampicin, is therefore low due to minimal hepatic metabolism (5 - 10 %) and low plasma protein binding.

## INDICATIONS:

**CIPLA DUOVIR** is indicated, as part of antiretroviral combination therapy, for the treatment of HIV-infected patients with progressive immunodeficiency ($CD4^+$ count $\leq$ 500 cells /$mm^3$).

**Post Exposure Prophylaxis in Adults following Occupational Exposure:**

The best prophylaxis against occupational exposure is adherence to universal precautions including, but not limited to, careful disposal of sharp objects such as needles and scalpels, and the use of protective barriers (such as gloves, eyeglasses, etc).

**CIPLA DUOVIR** is indicated for initial prophylactic treatment (until results of serology tests are available) in HIV negative adults whenever there has been contact with objects known to be, or strongly suspected to be, infected with HIV. This includes:

- percutaneous injury (from needles, bone fragments, instruments, etc.)
- exposure of broken skin (abrasions, cuts, eczema, etc.)
- exposure of mucous membranes including the eye.

The use of zidovudine for post exposure prophylaxis decreases the rate of infection and the combined use of lamivudine and zidovudine exhibits a greater reduction in viral load than either medicine used alone in HIV infected patients.

It is recommended to add a protease inhibitor to **CIPLA DUOVIR** in the following situations:

- when a large volume of inoculation has occurred
- when the source material has a high viral titre, or
- when inoculation has occurred from a patient with HIV resistant to zidovudine and/or lamivudine.

## CONTRA-INDICATIONS:

**CIPLA DUOVIR** is contraindicated in the following:

- patients with known hypersensitivity to lamivudine, zidovudine or any other component of the preparation,
- patients with abnormally low neutrophil counts (< 0.75 x $10^9$/l), or abnormally low haemoglobin levels (< 7.5 g/dl),
- children weighing less than 14 kg as an appropriate dose reduction for the weight of the child cannot be made.
- the combination of zidovudine with either ribavirin or stavudine is antagonistic *in vitro*. The concomitant use of either ribavirin or stavudine with **CIPLA DUOVIR** should be avoided (see **"INTERACTIONS"**).
- the combination of lamivudine with zalcitabine. The concomitant use of zalcitabine with **CIPLA DUOVIR** should be avoided (see **"INTERACTIONS"**).

## WARNINGS AND SPECIAL PRECAUTIONS:

In cases where dosage adjustment is necessary, it is recommended that separate preparations of zidovudine and lamivudine should be administered (see "**DOSAGE AND DIRECTIONS FOR USE**"). The medical practitioner should refer to the individual package inserts for these medicines in these cases.

***Opportunistic infections:*** Opportunistic infections and other complications of HIV infection may continue to develop in patients receiving **CIPLA DUOVIR** or any other antiretroviral therapy. Patients should therefore remain under close

clinical observation by medical practitioners experienced in the treatment of HIV infection. Regular monitoring of viral load and CD4 counts needs to be done.

***The risk of HIV transmission to others: CIPLA DUOVIR*** *or any other current antiretroviral therapy, has not been proven to prevent the risk of transmitting HIV to others through sexual contact or blood contamination. Patients should be advised that appropriate precautions against transmission should continue to be employed.*

***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.

***Haematological*****:** Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients on zidovudine and who have advanced symptomatic HIV disease. Haematological parameters should therefore be monitored carefully in patients on **CIPLA DUOVIR** (see "**CONTRA-INDICATIONS**"). These haematological adverse effects are not usually observed before four to six weeks of treatment. It is generally recommended that patients

with advanced symptomatic HIV disease should undergo blood tests at least on a biweekly basis for the first three months of therapy and thereafter at least monthly. Haematological adverse reactions occur infrequently in patients with early HIV disease. Blood tests may be performed less frequently (e.g. every one to three months) depending on the overall condition of the patient. When the haemoglobin level decreases by more than 25 % from baseline and the neutrophil count falls by more than 50 % from baseline, more frequent monitoring may be required. Additionally, dosage adjustment of zidovudine may be required in the following instances: severe anaemia or myelosuppression during treatment with **CIPLA DUOVIR**, or in patients with pre-existing compromised bone marrow, e.g. heamoglobin < 9 g/dl (5.59 mmol/l) or neutrophil count < 1.0 x $10^9$/l (see "**DOSAGE AND DIRECTIONS FOR USE**"). As dosage adjustment is not possible with **CIPLA DUOVIR**, zidovudine and lamivudine should be administered as separate preparations. Medical practitioners should then refer to the individual package inserts of these medicines for dosage specifications.

***Pancreatitis*:** Rare cases of pancreatitis have been reported in patients treated with lamivudine and zidovudine. A causal relationship with treatment, or whether it was due to underlying HIV disease, could not be established. If clinical signs, symptoms or laboratory abnormalities (abdominal pain, nausea, vomiting or elevated biochemical markers) suggestive of pancreatitis occur, treatment with **CIPLA DUOVIR** should be discontinued immediately 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 lamivudine and zidovudine is increased due to decreased clearance. The dose of lamivudine and zidovudine should therefore be adjusted (see **"DOSAGE AND DIRECTIONS FOR USE"**).

***Liver disease:*** **CIPLA DUOVIR** should be administered with caution to any patient with hepatomegaly, hepatitis, or other known risk factors for liver disease (particularly obese women). Should these patients receive **CIPLA DUOVIR**, they should be monitored closely while on therapy.

Use of **CIPLA DUOVIR** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **CIPLA DUOVIR** 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. Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

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 **CIPLA DUOVIR** 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 **CIPLA DUOVIR** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

**CIPLA DUOVIR** should be used with caution in patients with advanced liver cirrhosis as a result of chronic hepatitis B infection, as there is a low risk of rebound hepatitis if lamivudine is discontinued.

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be clarified. Therefore the concomitant use of ribavirin and zidovudine is not recommended and it should be taken into consideration the replacement of zidovudine in a combination antiretroviral therapy regimen if this is already established. This is especially vital in patients with a known history of zidovudine induced anaemia.

***Lactic acidosis / hyperlactataemia / severe hepatomegaly with steatosis:***

Use of **CIPLA DUOVIR** 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 agents 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 **CIPLA DUOVIR** to patients with known risk factors for liver disease.

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

Lactic acidosis, in the absence of hypoxaemia, including potentially fatal cases, and severe hepatomegaly with steatosis have been reported rarely in patients treated with zidovudine. It is not known whether there is a causal relationship with zidovudine, but these events have been reported in HIV-positive patients without AIDS. In the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology, treatment with **CIPLA DUOVIR** should be terminated.

***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.

***Self-medication:*** Concomitant use of self-administered medications should be discouraged during treatment with **CIPLA DUOVIR** and patients should be cautioned in this regard (see "**INTERACTIONS**").

***Fertility:*** Neither zidovudine nor lamivudine have shown evidence that they impair fertility in studies done in rats of both genders. There are no data available on the effect of these medicines on human female fertility. Zidovudine has not been shown to affect sperm count, morphology or motility in men.

***Pregnancy:*** In animal reproductive studies, both lamivudine and zidovudine were shown to cross the placenta and have been demonstrated to cause an increase in

early embryonic deaths in the rabbit (lamivudine), or rat and rabbit in the case of zidovudine. Lamivudine displayed no teratogenetic effects in animal studies. Zidovudine given at maternally toxic doses to rats during organogenesis resulted in a higher incidence of malformations. Foetal abnormalities were not observed at lower doses.

***Carcinogenesis and mutagenesis*:** A carcinogenic risk to humans can thus not be excluded, due to the animal carcinogenicity and mutagenicity data. Although the results of rodent carcinogenicity studies cannot always be extrapolated to humans, late-occurring vaginal tumours (appearing after 19 months of continuous daily oral dosing) have been observed in rodents following lifetime dosing with zidovudine. Whether these findings are relevant to both infected and uninfected infants exposed to zidovudine, is unknown. However, should a pregnant woman consider the use of **CIPLA DUOVIR** during pregnancy, she should be informed of these findings and any theoretical risk of carcinogenicity should be weighed against the proven therapeutic benefit. Neither zidovudine nor lamivudine have displayed mutagenesis in bacterial tests, but like many nucleoside analogues they have shown activity in *in vitro* mammalian tests. Lamivudine has not shown any genotoxicity in *in vivo* studies. AIDS patients receiving zidovudine treatment have displayed peripheral blood lymphocytes which contain higher numbers of chromosome breakages. It is not clear whether these findings have clinical implications.

***Effect on ability to drive and use machines:*** The effect of zidovudine or lamivudine on driving performance or the ability to operate machinery has not

been studied. Furthermore, based on the pharmacology of these medicines, a detrimental effect on such activities cannot be predicted. Nevertheless, the side-effect profiles of zidovudine and lamivudine (such as dizziness and other side effects that affect alertness) and the clinical status of the patient should be borne in mind when considering the patient's ability to drive or operate machinery.

**Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination in the treatment of HIV infection.**

**INTERACTIONS:**

Any interactions that have been identified with zidovudine and lamivudine individually may occur in **CIPLA DUOVIR**. Due to limited metabolism and plasma protein binding, and almost complete renal clearance, the likelihood of metabolic interactions with lamivudine is low. Similarly zidovudine has limited protein binding but is eliminated primarily by hepatic conjugation to an inactive glucuronidated metabolite.

**CIPLA DUOVIR** should not be taken with any other medicinal products containing lamivudine or emtricitabine.

The interactions listed below are by no means complete, but are representative of the classes of medicines where caution should be exercised.

**Interactions relevant to lamivudine:**

The possibility of interactions with other medicines administered concurrently with **CIPLA DUOVIR** should be considered, particularly those medicines which are eliminated mainly by active renal secretion, especially via the cationic transport system (e.g. trimethoprim). Other nucleoside analogues (e.g. zidovudine and didanosine) and various other medicines (e.g. ranitidine, cimetidine) are only partly eliminated by this mechanism and were shown not to interact with lamivudine.

**Refer to the "Pharmacokinetics" section for full details on the interactions between lamivudine and other antiretroviral agents.**

Prophylactic doses of ***co-trimoxazole*** have resulted in a 40 % increase in lamivudine exposure, due to the trimethoprim component. There is no interaction with the sulphamethoxazole component. However, no dosage adjustment of lamivudine is necessary unless the patient has renal impairment (see "**DOSAGE AND DIRECTIONS FOR USE**").

Patients who warrant concomitant administration of co-trimoxazole, should be monitored clinically. The concomitant administration of **CIPLA DUOVIR** with high doses of co-trimoxazole, as used in the treatment of *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis, should be avoided. Lamivudine, on the other hand, has no effect on the pharmacokinetics of co-trimoxazole at the doses studied.

Lamivudine may inhibit the intracellular phosphorylation of ***zalcitabine*** when the two medicines are used concomitantly and therefore **CIPLA DUOVIR** is not recommended to be used concurrently with zalcitabine (see **"CONTRA-INDICATIONS"**).

The combination of lamivudine with ***cladribine*** is not recommended as, *in vitro,* lamivudine inhibits the intracellular phosphorylation of cladribine resulting in a potential risk of the loss of efficacy of cladribine.

It is not recommended to co-administer lamivudine with intravenous ***ganciclovir*** or ***foscarnet*** until further information is available.

The metabolism of lamivudine does not involve CYP3A therefore interactions with medicines metabolised by this system (such as protease inhibitors) is unlikely.

**Interactions relevant to zidovudine:**

Although a slight increase in the $C_{max}$ (28 %) of zidovudine was observed when administered with ***lamivudine***, the overall exposure (AUC) was not significantly changed. Zidovudine, alternatively, has no effect on the pharmacokinetics of lamivudine.

The AUC of zidovudine is decreased by 48 % $\pm$ 34 % when co-administered with ***rifampicin***. However, the clinical significance of this is not known.

Even though zidovudine does not affect the pharmacokinetics of ***atovaquone***, atovaquone decreases the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC was increased by 33 % and peak plasma concentration of the metabolite was reduced by 19 %). Extra care should be taken in monitoring patients being treated with prolonged atovaquone treatment.

***Clarithromycin*** decreases the rate of absorption of zidovudine (found in **CIPLA DUOVIR**). This can be avoided by separating the administration of the two medicines by at least two hours.

***Valproic acid*** increases the zidovudine (found in **CIPLA DUOVIR**) AUC by 80 % and therefore any signs of zidovudine toxicity should be monitored in patients taking these medicines concurrently.

***Phenytoin*** concentrations should be carefully monitored in patients receiving **CIPLA DUOVIR** and phenytoin, as phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while a high level was noted in a single patient.

The concomitant use of ***paracetamol*** with zidovudine in a placebo-controlled trial was associated with an increased incidence of neutropenia, especially following chronic therapy. However, the available pharmacokinetic data indicate that neither the plasma levels of zidovudine nor its glucuronide metabolite is increased by paracetamol at the doses studied.

***Other medicines***, including, but not limited to, codeine, morphine, methadone, aspirin, indomethacin, ketoprofen, naproxen, cimetidine, clofibrate, dapsone, oxazepam, lorazepam and isoprinosine, may alter the metabolism of zidovudine by either directly inhibiting hepatic microsomal metabolism or competitive inhibition of glucuronidation. The possibilities of drug interactions should therefore be considered carefully before using such medicines, especially for chronic therapy, in combination with **CIPLA DUOVIR**.

The risk of adverse reactions to zidovudine may also increase with concomitant treatment, especially acute therapy, with potentially ***nephrotoxic or myelo-suppressive medicines*** (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, ganciclovir, interferon, flucytosine, vincristine, vinblastine and doxorubicin). Extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more of the medicines should be reduced, if concomitant therapy with **CIPLA DUOVIR** and any of these medicines is unavoidable.

The combination of zidovudine with either ***stavudine*** or ***ribavirin*** is antagonistic *in vitro*. The concomitant use of either of these medicines with **CIPLA DUOVIR** should therefore be avoided (see “**CONTRAINDICATIONS**”).

Refer to the "**Pharmacokinetics**" section for full details on the interactions between zidovudine and other antiretroviral agents.

The concomitant use of ***prophylactic antimicrobial therapy*** may have to be

considered, since some patients receiving **CIPLA DUOVIR** may continue to develop opportunistic infections. This named prophylaxis has included pyrimethamine, co-trimoxazole, aerosolised pentamidine and acyclovir. The limited data from clinical trials give no indication of a significantly increased risk of adverse reactions to zidovudine with these medicines.

According to limited data, ***probenecid*** increases the mean AUC and half-life of zidovudine by decreasing glucuronidation. Probenecid also reduces renal excretion of the glucuronide metabolite (and possibly zidovudine itself).

**PREGNANCY AND LACTATION:**

The safety of lamivudine in human pregnancy has not been established. Therefore, the administration of **CIPLA DUOVIR** during the first trimester of pregnancy is not recommended.

The use of zidovudine in pregnant women, with treatment of the newborn infant thereafter has been shown to reduce the rate of mother-to-child transmission of HIV. As there are no such data available for lamivudine, the administration of **CIPLA DUOVIR** during pregnancy should only be considered if the expected benefits outweigh any possible risks to the foetus or mother.
Mild and transient serum lactate level elevations have been reported possibly due to mitochondrial dysfunction in neonates and infants exposed *in utero* or *peri-partum* to NRTIs. The clinical significance of a rise in serum lactate levels is unknown. There have also been reports of developmental delay, seizures and

other neurological disease although a causal relationship between these events and exposure (*in utero* or *peri-partum* has not been established).

Both lamivudine and zidovudine are excreted into human milk at similar concentrations to those found in serum. Since they pass into breast milk it is recommended that mothers taking **CIPLA DUOVIR** do not breastfeed their infants.

## DOSAGE AND DIRECTIONS FOR USE:

**CIPLA DUOVIR** therapy should be initiated by a medical practitioner who has experience in the management of HIV infection.

To ensure that the entire dose is received, the tablets should be swallowed whole (without crushing). For those unable to swallow tablets they may be crushed and added to a small amount of liquid or semi-solid food and consumed immediately (see **"Pharmacokinetics"**).

**CIPLA DUOVIR** can be taken with or without food.

**Adults and children weighing at least 30 kg:**

The recommended dose is one **CIPLA DUOVIR** tablet twice daily.

**Children weighing between 21 kg and 30 kg:** The recommended oral dose of **CIPLA DUOVIR** is one-half (a half) tablet taken in the morning and one whole tablet taken in the evening.

**Children weighing from 14 kg to 21 kg:** The recommended oral dose of **CIPLA DUOVIR** is one-half (a half) tablet taken twice daily.

**For children weighing less than 14 kg:** Lamivudine and zidovudine should be taken as separate preparations as **CIPLA DUOVIR** is not suitable for these patients.

**Post Exposure Prophylaxis (PEP) following Exposure:**

The course of **CIPLA DUOVIR** should begin as soon as possible (preferably within 1 – 2 hours) after the exposure has occurred and continue until it is confirmed what the HIV-status of the source was. **Where the source is confirmed to be infected with HIV, it is recommended that the prophylactic source is continued for a period of 4 weeks.**

The following dosing guideline is based on recommendations as per the CDC (Centres for Disease Control) in the USA:

| **Duration** | **CIPLA DUOVIR Dosage** |
|---|---|
| Days 1 – 3 | 1 CIPLA DUOVIR tablet taken twice daily (equivalent to a daily dose of 300 mg lamivudine and 600 mg zidovudine). |
| Days 4 – 28 | 1 CIPLA DUOVIR tablet taken twice daily (equivalent to a daily dose of 300 mg lamivudine and 600 mg zidovudine). |

If a protease inhibitor is required to be added to the PEP regimen (see "**INDICATIONS"**), consult the CDC guidelines for dosing requirements.

If the source material is confirmed not to be infected with HIV, treatment should be discontinued immediately.

As **CIPLA DUOVIR** is used in combination with other antiretroviral agents, the package inserts of these particular agents should be consulted for relevant information.

In situations where discontinuation of therapy with one of the active ingredients of **CIPLA DUOVIR**, or dose reduction, is necessary, separate preparations of lamivudine and zidovudine, which are available in tablets / capsules and oral solution, should be used.

**Renal impairment:**

Due to decreased clearance in patients with renal impairment, the concentrations of lamivudine and zidovudine are elevated. Therefore as dosage adjustment of these may be required, it is advised that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance $\leq$ 50 ml/min). The package insert for separate preparations must be consulted for full details of these dosage adjustments.

**Hepatic impairment:**

The influence of hepatic impairment on lamivudine levels has not been fully elucidated. Lamivudine clearance is predominantly renal. Based on preliminary safety data, dosage adjustment is not necessary. Lamivudine should be used with caution in patients with hepatomegaly or other risk factors for hepatic disease.

However, zidovudine accumulation may occur in patients with hepatic impairment due to decreased glucuronidation, based on limited data in patients with cirrhosis.

Therefore, it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with severe hepatic impairment, as dosage adjustments of zidovudine may be necessary. The package insert for zidovudine must be consulted for full prescribing details and dosage adjustments.

**Dosage adjustments in patients with haematological adverse reactions:**
It may be necessary to adjust the dosage of zidovudine if the haemoglobin level falls below 9 g/dl or 5.59 mmol/l or the neutrophil count drops below 1.0 x $10^9$ /l (see "**CONTRA-INDICATIONS**"). Patients with poor bone marrow reserve prior to treatment, particularly in patients with advanced HIV disease, are more prone to these haematological effects. Separate preparations of zidovudine and lamivudine should be used, as **CIPLA DUOVIR** dosage cannot be adjusted. Medical practitioners should refer to the individual package inserts of these medicines for full prescribing details.

**Dosage in the elderly:**
Special care is advised in the elderly due to age-associated changes, such as a decrease in renal function and changes in haematological parameters.

**SIDE-EFFECTS:**
During therapy for HIV disease with lamivudine and zidovudine separately or when used in combination, adverse events have been reported. With many of these events it is unclear whether they are related to lamivudine, zidovudine or to the wide range of other medicines used in the management of HIV disease, or are due to the underlying disease process.

Since **CIPLA DUOVIR** contains lamivudine and zidovudine, the type and severity of adverse reactions associated with the separate compounds may be expected. There is no evidence of synergistic toxicity due to concomitant administration of the two antiretrovirals.

**<u>Lamivudine</u>:**

***Blood and lymphatic system disorders:***

*Less frequent*: Anaemia and neutropenia (both occasionally acute) have occurred when used in combination with zidovudine. Thrombocytopenia, pure red cell aplasia.

***Metabolism and nutrition disorders:***

*Frequent*: hyperlactataemia

*Less frequent*: lactic acidosis (see "**WARNINGS AND SPECIAL PRECAUTIONS").** Lipodystrophy [redistribution/accumulation of body fat (see "**WARNINGS AND SPECIAL PRECAUTIONS"**).

***Nervous system disorders:***

*Frequent*: Headache, insomnia.

*Less frequent*: Cases of peripheral neuropathy (or paraesthesia) have been recorded, although no relationship to the dose of lamivudine has been reported.

***Respiratory, thoracic and mediastinal disorders:***

*Frequent*: Nasal symptoms, cough.

***Gastrointestinal disorders:***

*Frequent*: Nausea, vomiting, abdominal pain or cramps, diarrhoea.

*Less frequent*: Cases of pancreatitis have been recorded, although no relationship to the dose of lamivudine has been recorded. Rises in serum amylase have been reported.

***Hepato-biliary disorders:***

*Less frequent*: Transient rises in liver enzymes (AST, ALT) have been reported.

***Skin and subcutaneous tissue disorders:***

*Frequent*: Rash, alopecia.

***Musculoskeletal, connective tissue and bone disorders:***

*Frequent:* Musculoskeletal pain, arthralgia.

*Less frequent:* rhabdomyolysis.

***General disorders and administrative site conditions:***

*Frequent:* Fatigue, malaise, fever.

**<u>Zidovudine</u>:**

***Blood and lymphatic system disorders:***

*Frequent*: Anaemia (which may require transfusions), neutropenia and leucopenia, have been reported as the most serious adverse

reactions.

These adverse reactions occur more often at higher dosages (1200 - 1500 mg/day) and in patients with advanced HIV disease (especially when the bone marrow reserve is poor prior to treatment), and particularly in patients with $CD4^+$ cell counts < 100 /$mm^3$. A reduction in the dosage or discontinuation of therapy may become essential (see "**DOSAGE AND DIRECTIONS FOR USE**"). Neutropenia incidence was also raised in patients whose neutrophil counts, haemoglobin levels and serum vitamin $B_{12}$ levels were low at the start of zidovudine therapy, and in those patients who are concurrently taking paracetamol (see "**INTERACTIONS**").

*Less frequent*: Pancytopenia with marrow hypoplasia, isolated thrombocytopenia, aplastic anaemia.

***Metabolism and nutrition disorders:***

*Frequent:* hyperlactatemia

*Less frequent*: lactic acidosis in the absence of hypoxaemia (see "**WARNINGS AND SPECIAL PRECAUTIONS"),** anorexia**.** Lipodystrophy [redistribution / accumulation of body fat (see "**WARNINGS AND SPECIAL PRECAUTIONS"**).

***Psychiatric disorders:***

*Less frequent*: anxiety, depression.

***Nervous system disorders:***

*Frequent:* Headache, dizziness.

*Less frequent:* Cases of peripheral neuropathy (or paraesthesia), insomnia, somnolence, loss of mental acuity, convulsions.

Severe headache and insomnia were more common in zidovudine-treated patients with advanced HIV disease.

***Cardiac disorders:***

*Less frequent:* cardiomyopathy.

***Respiratory, thoracic and mediastinal disorders:***

*Less frequent*: Cough, dyspnoea.

***Gastrointestinal disorders:***

*Frequent*: Nausea, anorexia, vomiting, dyspepsia, abdominal pain. Anorexia and vomiting were more common in zidovudine-treated patients with early HIV disease.

*Less frequent*: Flatulence, diarrhoea, pancreatitis, taste perversion / disturbance.

***Hepatobiliary disorders:***

*Frequent*: raised blood levels of liver enzymes and bilirubin.

*Less frequent*: liver disorders such as severe hepatomegaly with steatosis.

***Skin and subcutaneous tissue disorders:***

*Frequent*: Rash.

*Less frequent*: Sweating, urticaria, pruritus. Skin, nail and oral mucosa pigmentation.

***Musculoskeletal, connective tissue and bone disorders:***

*Frequent*: Myalgia. Myalgia was more common in zidovudine-treated patients with advanced HIV disease.

*Less frequent*: myopathy.

***Renal and urinary disorders:***

*Less frequent*: Urinary frequency.

***Reproductive system and breast disorders:***

*Less frequent*: gynaecomastia

***General disorders and administrative site conditions:***

*Frequent*: Fever, malaise, asthenia. Malaise and asthenia were more common in zidovudine-treated patients with early HIV disease.

*Less frequent*: Influenza-like syndrome, chills, generalised pain, chest pain.

Apart from nausea, which was significantly more common in patients receiving zidovudine in all studies, the other frequently reported adverse events were not consistently reported to be more common than in the placebo recipients. The data available from both placebo-controlled and open-labelled studies indicate that the prevalence of nausea and other frequently reported clinical adverse

events consistently decrease over time during the first few weeks of therapy with zidovudine.

The incidence of the less frequent adverse events was shown to be similar in both zidovudine- and placebo-treated patients.

In patients receiving open-label therapy with zidovudine, convulsions and other cerebral events have also been recorded. The beneficial effect of zidovudine on HIV-associated neurological disorders has overall been proven by the weight of evidence.

A reduction or suspension of zidovudine therapy may assist in the assessment and management of these conditions, if the severity of the symptoms warrants it. **CIPLA DUOVIR** should be discontinued and separate preparations of zidovudine and lamivudine should be administered, if symptoms become intolerable (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

## KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no experience of **CIPLA DUOVIR** overdosage. However, there are limited data available on the sequelae of ingestion of acute overdoses of zidovudine and lamivudine in humans. All patients recovered and no fatalities occurred. No specific signs or symptoms are attributed to such overdosage.

***Treatment of overdosage:***

Should overdosage occurs, the patient should be carefully monitored for evidence of toxicity (see "**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**"), and the necessary supportive treatment should be applied. Continuous haemodialysis could be used in the treatment of overdosage, since lamivudine is dialysable, although this has not been investigated. Haemodialysis and peritoneal dialysis enhance the elimination of the glucuronide metabolite of zidovudine, but appear to have a limited effect on elimination of zidovudine itself. Medical practitioners should refer to the individual package inserts of lamivudine and zidovudine for further details. Patients, in whom intentional overdose is confirmed or suspected, should be referred for psychiatric consultation.

## IDENTIFICATION:

White coloured, film-coated, oblong, biconvex tablet with “DVR” embossed on one side and plain on the other side.

## PRESENTATION:

**CIPLA DUOVIR** tablets: are available in aluminium foil blister strips of 10 tablets, packed in 60's and/or 100’s, or sixty (60) tablets packed in a white-coloured, high density polyethylene (HDPE) bottle containing a silica gel bag and cotton wool, and closed with a milky-coloured screw cap, packed in a carton.

## STORAGE INSTRUCTIONS:

Store below 25˚C. Protect from light.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBER**:

A40/20.2.8/0244

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

CIPLA MEDPRO MANUFACTURING (PTY) LTD

1474 South Coast Road

Mobeni

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**DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

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