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.

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.8 Antiviral agents.

PHARMACOLOGICAL ACTION:
Pharmacodynamics:
Zidovudine and lamivudine are both selective inhibitors 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.

Pharmacokinetics:
Absorption and distribution: 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.
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.
Zidovudine and lamivudine penetrate the central nervous system and reach the cerebrospinal fluid (CSF).

Metabolism and excretion: 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.

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 adults and children over 12 years of age with progressive immunodeficiency ($CD4^+$ count $\leq$ 500 cells /mm^3).

CONTRAINDICATIONS:
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 below the age of 12 years due to insufficient data,
- 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.

WARNINGS:
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.

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.*

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 "**CONTRAINDICATIONS**"). 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.

Gastrointestinal: 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 suggestive of pancreatitis occur, treatment with **CIPLA DUOVIR** should be discontinued immediately.

Metabolic: 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.

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 (see "**Special Precautions**"). 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.

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.

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, didanosine and zalcitabine) 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.

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

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.

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, 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.

According to studies in lactating rats, lamivudine and zidovudine, administered orally, were excreted in the milk. It is not known if zidovudine or lamivudine is excreted in human milk. Since they may pass into breast milk it is recommended that mothers taking **CIPLA DUOVIR** should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE:
Adults and children over the age of 12 years:

Recommended dose: One **CIPLA DUOVIR** tablet twice daily, with or without food.

CIPLA DUOVIR therapy should be initiated by a medical practitioner who has experience in the management of HIV infection.
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 "**CONTRAINDICATIONS**"). 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 AND SPECIAL PRECAUTIONS:
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.

Lamivudine:
Haematological and lymphatic system disorders:
The following side-effects have been reported and frequencies are unknown.
Anaemia and neutropenia (both occasionally acute) have occurred when used in combination with zidovudine.
Thrombocytopenia has been reported.

Neuropsychiatric disorders:
The following side-effects have been reported and frequencies are unknown.
Headache, insomnia.
Cases of peripheral neuropathy (or paraesthesia) have been recorded, although no relationship to the dose of lamivudine has been reported.

Respiratory disorders:
The following side-effects have been reported and frequencies are unknown.
Nasal symptoms, cough.

Skin and appendages disorders:
The following side-effects have been reported and frequencies are unknown.
Rash, alopecia.

Gastrointestinal disorders:
The following side-effects have been reported and frequencies are unknown.
Nausea, vomiting, abdominal pain or cramps, diarrhoea.
Cases of pancreatitis have been recorded, although no relationship to the dose of lamivudine has been recorded.
Rises in serum amylase have been reported.

Hepatobiliary disorders:
The following side-effects have been reported and frequencies are unknown.
Transient rises in liver enzymes (AST, ALT) have been reported.

Musculoskeletal disorders:
The following side-effects have been reported and frequencies are unknown.
Musculoskeletal pain, arthralgia and rarely rhabdomyolysis.

General disorders:
The following side-effects have been reported and frequencies are unknown.
Fatigue, malaise, fever.

Zidovudine:
Haematological and lymphatic system disorders:
The following side-effects have been reported and frequencies are unknown.

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**").

The following frequent and less frequent adverse events were reported in large placebo-controlled clinical trails:

Neuropsychiatric disorders:
Frequent: Headache, paraesthesia, insomnia. Severe headache and insomnia were more common in zidovudine-treated patients with advanced HIV disease.
Less frequent: Loss of mental acuity, somnolence, dizziness, anxiety, depression.

Special senses disorders:
Less frequent: Taste perversion.

Respiratory 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.

Skin and appendages disorders:
Frequent: Rash.
Less frequent: Sweating, urticaria, pruritus.

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

Urogenital disorders:
Less frequent: Urinary frequency.

General disorders:
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.

The relationship between the following events, which have been reported on, and the use of zidovudine is difficult to evaluate if the medically complicated situations, which characterise advanced HIV disease, is considered:

Haematological and lymphatic system disorders:
The following side-effects have been reported and frequencies are unknown.
Pancytopenia with marrow hypoplasia and isolated thrombocytopenia.

Metabolic disorders:
The following side-effects have been reported and frequencies are unknown.
Lactic acidosis in the absence of hypoxaemia.

Gastrointestinal and hepatobiliary disorders:
The following side-effects have been reported and frequencies are unknown.
Pancreatitis, liver disorders such as severe hepatomegaly with steatosis, raised blood levels of liver enzymes and bilirubin.

Musculoskeletal disorders:
The following side-effects have been reported and frequencies are unknown.
Myopathy.

Skin, appendages and mucosal disorders:
The following side-effects have been reported and frequencies are unknown.
Skin, nail and oral mucosa pigmentation.

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 "**Special Precautions**").

Special Precautions:
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.
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.

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.

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

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.

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.

Lamivudine did not show any potential for carcinogenesis in long-term oral carcinogenicity studies in rats and mice. In animals treated with zidovudine, treatment-related effects were limited to the late appearance of vaginal neoplasms. Whether these tumours are relevant to humans is uncertain, and any theoretical risk of carcinogenicity should be weighed against the proven therapeutic benefit.

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 and the clinical status of the patient should be borne in mind when considering the patient's ability to drive or operate machinery.

Pancreatitis: Pancreatitis has been observed in some patients receiving **CIPLA DUOVIR.** However it is unclear whether this is due to **CIPLA DUOVIR** or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **CIPLA DUOVIR** until diagnosis of pancreatitis is excluded.

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.

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 LIFE SCIENCES (PTY) LIMITED,
Rosen Heights, Rosen Park,
Bellville, 7530, R.S.A.

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