REGISTERED PATIENT INFORMATION FOR CIPLA-ZIDOVUDINE:

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-ZIDOVUDINE (Capsules)

COMPOSITION OF THE MEDICINE, THAT IS, WHAT THIS MEDICINE CONTAINS:

The active substance is zidovudine 100 mg per capsule.

CIPLA-ZIDOVUDINE (Capsules) *contain*:

Preservative: Bronopol 0.011 % m/m. The other ingredients are microcrystalline cellulose, sodium starch glycollate, magnesium stearate, maize starch, magnesium stearate, colloidal silicon dioxide, purified talc, gelatin, povidone, sodium lauryl sulphate and titanium dioxide.

APPROVED INDICATION AND USE, THAT IS, WHAT IS THIS MEDICINE USED FOR:

CIPLA-ZIDOVUDINE (Capsules) are used in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults, children and mothers who are not breast-feeding and for the prophylaxis of maternal-foetal HIV transmission in HIV positive pregnant women of over 14 week gestation and their own newborn infants.

INSTRUCTIONS BEFORE YOU TAKE CIPLA-ZIDOVUDINE (CAPSULES):

Tell your doctor if you have ever had any unusual or allergic reaction to zidovudine. Also tell your health care professional if you are allergic to any other substances, such as foods, preservatives, or dyes.

CIPLA-ZIDOVUDINE (Capsules) can cause serious side-effects in any patient. Therefore, it is especially important that you discuss with your child's doctor the good that this medicine may do as well as the risk of using it. Your child must be carefully followed, and frequently seen, by the doctor while he or she is taking zidovudine.

Do not take CIPLA-ZIDOVUDINE (Capsules)**:**

If you have known hypersensitivity to zidovudine or any other ingredients of the formulation.

Take special care with CIPLA-ZIDOVUDINE (Capsules)

The presence of other medical problems may affect the use of zidovudine. Make sure to tell your doctor if you have any other medical problems, especially:

- Anemia or other blood problems
- Liver disease
- Low amounts of folic acid of vitamin 812 in the blood
- At risk of liver disease
- Obesity
- Taking medicines called nucleosides for a long time

Taking CIPLA-ZIDOVUDINE (Capsules) **with food and drink:**

CIPLA-ZIDOVUDINE (Capsules) can be taken with or without food.

PREGNANCY AND BREAST-FEEDING:

If you may become pregnant or are pregnant or breast feeding your baby while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice. The safety of **CIPLA-ZIDOVUDINE** (Capsules) has not been established in human pregnancy. Since zidovudine may pass into breast milk, breastfeeding by mothers taking **CIPLA-ZIDOVUDINE** (Capsules) are not recommended. Breast-feeding is usually not recommended in patients with HIV infection because of the risk of passing the HIV to the infant.

TAKING OTHER MEDICINES WITH CIPLA-ZIDOVUDINE (Capsules)

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. When you take zidovudine it is especially important that your health care professional knows if you are taking any of the following:

- Amphotericin B by injection
- Antineoplastics (cancer medicine)
- Antithyroid agents (medicines for an overactive thyroid)
- Azathioprine
- Chloramphenicol
- Colchicine
- Cyclophosphamide
- Flucytosine
- Ganciclovir
- Interferon
- Mercaptopurine
- Methotrexate
- Plicamycin

Caution should be taken if these medicines and zidovudine are used together, as they may make anemia or other blood problems worse.

- Clarithromycin -may decrease the amount of zidovudine in the blood.
- Combination drugs that contain zidovudine- may increase the amount of zidovudine in the blood, increasing the chance of side effects.
- Probenecid- may increase the amount of zidovudine in the blood, increasing the chance of side effects.

- Doxorubicin or ribavirin - may cause zidovudine to be less effective.

If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of **CIPLA-ZIDOVUDINE** (Capsules) with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional, for advice.

INSTRUCTIONS ON HOW TO TAKE THE MEDICINE CIPLA-ZIDOVUDINE (Capsules):

Always take **CIPLA-ZIDOVUDINE** (Capsules) exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure of the dosage of **CIPLA-ZIDOVUDINE** (Capsules). The usual dose is:

Recommended dosage in adults:

CIPLA-ZIDOVUDINE (Capsules) in combination with other antiretroviral agents:

500 or 600 mg daily in two or three divided doses.

More than 1000 mg daily in divided doses has been used. The effectiveness of dosages lower than 1000 mg daily in the treatment or prevention of HIV-associated neurological dysfunction is unknown.

For dosages of other antiretroviral agents used in combination therapy in advanced HIV infection: Please consult the package inserts of the individual agents.

Recommended dosage in children 3 months to 12 years of age:

CIPLA-ZIDOVUDINE in combination with other antiretroviral agents:

360 to 480 mg/m^2 daily in three or four divided doses.

For the treatment or prevention of HIV-associated neurological dysfunction, the effectiveness of dosages less than 720 mg/m^2 daily, i.e. 180 mg/m^2 every six hours, is unknown.

The maximum dosage should not exceed 200 mg every six hours.

Recommended dosage in the prevention of mother-to-foetus transmission:

Pregnant women over 14 weeks of gestation:

500 mg orally per day, i.e. 100 mg five times per day, until the beginning of labour. During labour and delivery zidovudine should be administered intravenously at 2 mg/kg body mass over 1 hour, followed by a continuous intravenous infusion at 1 mg/kg per hour until the umbilical cord is clamped.

The newborn infants: starting within 12 hours after birth until at 6 weeks of age:

2 mg/kg body mass orally every 6 hours. Infants unable to receive oral dosing should be given zidovudine intravenously at 1,5 mg/kg body mass, infused over 30 minutes every 6 hours

Dosage adjustments in patients with haematological toxicity:

Dosage reduction or interruption of **CIPLA-ZIDOVUDINE** therapy may be necessary in patients whose haemoglobin level falls to between 7,5 g/dl

(4,65 mmol/l) and 9 g/dl (5,59 mmol/l) or whose neutrophil count falls to between 0,75 x 10^9/l and 1,0 x 10^9/l.

Dosage adjustments of CIPLA-ZIDOVUDINE in combination with other antiretroviral medicines:

Dosage adjustments for each medicine should follow the dosing guidelines for the individual medicine.

For severe adverse events, where the causative agent is unclear, or those persisting after dose interruption or reduction of one medicine, the other medicine should also be interrupted or dose reduced.

The medical practitioner should refer to the package insert of the other antiretroviral medicines for a description of known adverse reactions.

Dosage in the elderly:

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. Due to age-associated changes, such as the decrease in renal function and alterations in haematological parameters in this age group, special care is advised with the use of **CIPLA-ZIDOVUDINE**.

Appropriate monitoring of these patients before and during **CIPLA ZIDOVUDINE** therapy is advised.

Dosage in renal impairment:

Patients with advanced renal failure have a 50 % higher maximum plasma concentration of zidovudine compared to healthy individuals. Systemic

exposure to zidovudine (measured as the area under the time-concentration curve) is increased 100 %; the half-life is not significantly altered. There is substantial accumulation of the major glucuronide metabolite in renal failure, but this does not appear to cause toxicity.

In patients with severe renal impairment on peritoneal or haemodialysis, daily dosages of 300 to 400 mg in 3 to 4 divided dosages should be appropriate. Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. Haemodialysis and peritoneal dialysis have no significant effect on the elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

Dosage in hepatic impairment:

There are only limited data available, therefore precise dosage recommendations cannot be made, but dosage adjustments may be necessary. Data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Medical practitioners will need to monitor for signs of intolerance and adjust the dose and/or increase the interval between doses as appropriate.

If you have the impression that the effect of **CIPLA-ZIDOVUDINE** (Capsules) is too strong or too weak, talk to your doctor or pharmacist.

If you take more CIPLA-ZIDOVUDINE CAPSULES than you should:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, seek help at the nearest hospital or poison control centre.

In the event of overdosage, the patient should be monitored, and standard supportive treatment applied as required.

If you forget to take CIPLA-ZIDOVUDINE CAPSULES:

If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

POSSIBLE SIDE EFFECTS CIPLA-ZIDOVUDINE CAPSULES:

CIPLA-ZIDOVUDINE (Capsules) can have side effects.

Not all side effects reported for this medicine are included in this leaflet.

Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.

The adverse event profile appears to be similar for adults and children.

Side-effects:

Haematological system:

The most serious adverse reactions include anaemia, usually occurring after six weeks of therapy but occasionally earlier and often requiring transfusions; neutropenia, usually occurring at any time after 4 weeks of therapy but sometimes earlier; and leucopenia, which is usually secondary to neutropenia.

Thrombocytopenia and pancytopenia with marrow hypoplasia have also been reported.

Anaemia, neutropenia, and leucopenia occur more frequently at higher dosages of 1 200 to 1 500 mg/day, and in patients with advanced HIV disease, especially where there is poor bone marrow reserve rior to treatment, and particularly in patients with low T4 (T-helper) cell counts (less than 100/mm^3). Dosage reduction or cessation of therapy may become necessary. The incidence of neutropenia was also increased in patients with pre-existing neutropenia or anaemia, those with low vitamin B_{12} levels and those taking paracetamol concomitantly. The following events have also been reported in patients treated with **CIPLA-ZIDOVUDINE**. The relationship between these events and the use of **CIPLA-ZIDOVUDINE** may be difficult to evaluate, particularly in medically complicated situations that characterize advanced HIV disease.

A reduction in dose or suspension of **CIPLA-ZIDOVUDINE** therapy may be warranted in the management of these conditions.

Gastro-intestinal disorders:

Nausea, vomiting, pigmentation of the oral mucosa, abdominal pain, dyspepsia, anorexia, diarrhoea, flatulence.

Hepatobilliary disorders:

Liver disorders such as severe hepatomegaly with steatosis, raised blood levels of liver enzymes and bilirubin, pancreatitis.

Metabolic/Endocrine disorders:

Lactic acidosis in the absence of hypoxia (see Special Precautions).

Musculoskeletal system disorders:

Myalgia, myopathy, asthenia. Psychiatry disorders: Anxiety, depression.

Skin and appendages:

Nail and skin pigmentation, rash, urticaria, pruritus, sweating.

Respiratory system disorders:

Dyspnoea, cough, chest pain.

Central and peripheral nervous system disorders:

Headache, dizziness, insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions.

Genitourinary system disorders:

Urinary frequency, gynaecomastia.

Special senses disorders:

Taste perversion.

Body as whole:

Fever, malaise, generalised pain, chills, influenza-like syndrome.

Special precautions:

Haematological toxicity:

Haematological parameters should be carefully monitored. It is recommended that blood tests be performed at least every two weeks for the first three months of therapy and at least once a month thereafter for patients with advanced symptomatic HIV disease. Haematological toxicity is less frequent in patients with early HIV disease, where bone marrow reserve is generally good. Depending on the overall condition of the patient, blood tests may be

performed less often, for example every one to three months. If the haemoglobin level falls to between 7,5 g/dl (4.65 mmol/l) and 9 g/dl (5,59 mmol/l), or the neutrophil count falls to between 0,75 x 10^9/l and 1,0 x 10^9/l, the daily dosage may be reduced until there is evidence of marrow recovery. Alternatively, recovery may be enhanced by a brief 2 to 4 weeks interruption of CIPLA-ZIDOVUDINE therapy.

Marrow recovery is usually observed within 2 weeks after which time **CIPLA-ZIDOVUDINE** therapy may be restarted at a reduced dose. Dosage adjustments do not necessarily eliminate the need for transfusions in patients with significant anaemia (see **Side-effects**).

Lactic acidosis/severe hepatomegaly with steatosis:

Long-term use of **CIPLA-ZIDOVUDINE** can result in potentially fatal lactic acidosis. Symptomatic hyperlacticaemia and lactic acidosis are uncommon. 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 mmoi/L: monitor regularly, and be alert for clinical signs.

-Lactate 5-10 mmoi/L without symptoms: monitor closely.

-Lactate 5-10 mmoi/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).

-Lactate> 10 mmoi/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 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.
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of **CIPLA-ZIDOVUDINE** alone or in combination in the treatment of HIV infection.

Most cases were women. Caution should be exercised when administering **CIPLA-ZIDOVUDINE** to patients with known risk factors to liver disease.
Treatment with **CIPLA-ZIDOVUDINE** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Prevention of mother-to-foetus transmission:
The long-term consequences of *in utero* and infant exposure to **CIPLA-ZIDOVUDINE** are unknown.
Low haemoglobin concentrations have been reported in infants exposed to zidovudine for this indication, but transfusion was not required. Anaemia resolved within 6 weeks after completion of zidovudine therapy.

Lactation:

To avoid the transmission of HIV to their infants, women infected with HIV should not breast-feed.

STORING AND DISPOSING OF CIPLA-ZIDOVUDINE CAPSULES:

Store below 25 °C, protected from light. Keep the blister strips in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

Keep all medicines out of the reach and sight of children. Do not use after the expiry date stated on the label. Return all unused medicine to your pharmacist.

IDENTIFICATION:

A hard gelatine capsule with a light blue cap and white body, with ZVR 100 printed straight on both cap and body with black ink.

PRESENTATION:

White HDPE plastic container of 100 or 1000 capsules closed with a milky-coloured screw cap packed in a carton, OR, aluminium strip pack of 10 capsules, packed in boxes of 100 and 500 capsules.

REGISTRATION NUMBER:

34/20.2.8/0142

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

CIPLA MEDPRO (PTY) LTD

Building 9, Parc du Cap, Mispel Street, Bellville, 7530. RSA

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