REGISTERED PACKAGE INSERT FOR CIPLA-ZIDOVUDINE:

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-ZIDOVUDINE (Capsules)

COMPOSITION:

Each capsule contains zidovudine 100 mg.

Preservative: Bronopol 0.011 % m/m.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents.

PHARMACOLOGICAL ACTION:

Zidovudine, a thymidine nucleoside analogue, is an antiviral medicine with *in vitro* activity against retroviruses, such as the human immunodeficiency virus (HIV) and the Human T lymphotropic virus (HTLV)-I. Following diffusion into both infected and uninfected host cells, zidovudine is phosphorylated to the monophosphate derivative by cellular thymidine kinase. The phosphorylation of zidovudine-monophosphate to the diphosphate derivative and to the zidovudine-triphosphate is in turn catalysed by cellular thymidylate kinase and unspecific kinases, respectively.

Zidovudine-triphosphate is a competitive inhibitor of, and a substrate for, reverse transcriptase with respect to the thymidine triphosphate (TTP) nucleotide. The incorporation of zidovudine-triphosphate into the proviral DNA chain blocks further chain formation and results in chain termination. Zidovudine-triphosphate has greater affinity (approximately 100-fold) for HIV reverse transcriptase than for human DNA polymerase alpha.

Combination therapy with lamivudine:

Zidovudine monotherapy leads to development of *in vitro* and *in vivo* resistance to zidovudine.

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

Additive or synergistic activity in cell culture has been demonstrated in medicine combination studies of zidovudine with indinavir, zalcitabine, didanosine, delaviridine, lamivudine, saquinavir, ritonavir, nevirapine, and interferon-alpha.

In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

Pharmacokinetics:

Zidovudine is well absorbed from the gut, and oral bioavailability is approximately 60 to 70 %. Absorption varies in HIV-infected patients and is retarded after food intake.

Cerebrospinal fluid concentrations vary, but average approximately 53 % of those in plasma in adults, and 24 % of those in plasma in children.

The plasma elimination half-life is approximately 0.9 to 1.5 hours. Zidovudine undergoes first-pass hepatic metabolism and is converted to its 5'-O-glucuronide metabolite, which has a similar plasma elimination half-life, but lacks anti-HIV activity. The recovery of zidovudine and its glucuronide metabolite in urine, after oral administration, averages 14 % and 75 %, respectively. Renal clearance involves both glomerular filtration and tubular secretion. Two- to threefold increases in plasma levels and plasma elimination half-life occur in liver cirrhosis. There are no clinically significant pharmacokinetic interactions when zidovudine is given concomitantly with the following antiretroviral medicines:

- *Nucleoside reverse transcriptase inhibitors* (NRTIs)
  (zalcitabine, didanosine and abacavir)
- *Non-nucleoside reverse transcriptase inhibitors* (NNRTIs)
  (nevirapine and efavirenz)
- *Protease inhibitors*
  (indinavir sulphate, saquinavir mesylate, ritonavir, amprenavir, and nelfinavir)

Pharmacokinetics in children:

Zidovudine clearance is significantly reduced in children less than one month of age. In children over the age of five months, the pharmacokinetic profile of zidovudine is similar to that in adults.

INDICATIONS:

CIPLA-ZIDOVUDINE is indicated 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.

For the prophylaxis of maternal-foetal HIV transmission in HIV positive pregnant women of over 14 week gestation and their own newborn infants.

CONTRA-INDICATIONS:

- Hypersensitivity to any of the ingredients.
- Abnormally low neutrophil cell counts (less than 0.75 x 10^9/litre).
- Abnormally low haemoglobin levels (less than 7.5 g/decilitre).
- Co-administration with stavudine (d4T) and ribavirin (see **INTERACTIONS**).
- **Breast-feeding**.
- The safety of **CIPLA-ZIDOVUDINE** for the mother and foetus during the first trimester of pregnancy has not been established.

WARNINGS:

Patients should be warned about the concomitant use of self-administered medicines (see **INTERACTIONS**).

PATIENTS SHOULD BE ADVISED THAT CIPLA-ZIDOVUDINE THERAPY HAS NOT BEEN SHOWN TO REDUCE THE RISK OF TRANSMISSION OF HIV TO OTHERS THROUGH SEXUAL CONTACT OR BLOOD CONTAMINATION.

Pregnant women considering the use of **CIPLA-ZIDOVUDINE** during pregnancy for prevention of HIV transmission to their infants should be advised that transmission might still occur despite therapy.

CIPLA-ZIDOVUDINE is not a cure for HIV infection and patients remain at risk of developing illnesses associated with immune suppression, including opportunistic infections and neoplasms.

In patients with early HIV disease on long-term treatment the risk of lymphoma development is unknown as data on the development of neoplasms, including lymphomas are limited.

Patients receiving combination therapy may also continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close observation by medical practitioners experienced in the treatment of patients with HIV-associated diseases.

INTERACTIONS:

As zidovudine is primarily eliminated by hepatic conjugation to its inactive glucuronidated metabolite, medicines that are primarily eliminated by hepatic metabolism, especially by glucuronidation, may have the potential to inhibit the metabolism of **CIPLA-ZIDOVUDINE**. The interactions listed below, though not exhaustive, are representative of the classes of medicines where caution should be exercised:

- Caution must be exercised in the concomitant use of self-administered medicines.

- Phenytoin levels should be carefully monitored in patients receiving both medicines. There is a risk of either sub-therapeutic or toxic levels of phenytoin resulting from co-administration of these medicines.
- Aspirin, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone, and isoprinosine may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism especially in chronic combination therapy.
- Concomitant therapy with potentially nephrotoxic, or myelosuppressive medicines, such as dapsone, systemic pentamidine, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine, and doxorubicin, may also increase the risk of toxicity with **CIPLA-ZIDOVUDINE**. If concomitant therapy with any of these medicines is necessary, then extra care should be employed in monitoring renal function and haematological parameters and, if required, the dosage of one or both medicines should be reduced.
- There is an *in vitro* antagonistic interaction between zidovudine and either ribavirin or stavudine. The concomitant use of either of these medicines with zidovudine should be avoided.
- Some patients receiving zidovudine may continue to experience opportunistic infections and concomitant use of prophylactic antimicrobial therapy may have to be considered. There is limited data that indicates no increased risk of toxicity with co-trimoxazole, aerosolised pentamidine, pyrimethamine and acyclovir.

- There is limited data suggesting that probenecid increases the mean half-life and the area under the time-concentration curve (AUC) of zidovudine, by reducing glucuronidation. Renal excretion of the inactive glucuronide metabolite, and possibly zidovudine itself, is reduced in the presence of probenecid.
- There is limited data suggesting that co-administration of zidovudine and rifampicin decreases the AUC of zidovudine. The clinical significance of this is not known.
- There is a modest increase in C_{max} of zidovudine when administered with lamivudine, however overall exposure to zidovudine (AUC) is not altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.
- See under **Pharmacokinetics** for information on the effect on the pharmacokinetics of zidovudine when administered with other antiretroviral medications.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (see **CONTRA-INDICATIONS**).

The long-term consequences of *in utero* and infant exposure to **CIPLA-ZIDOVUDINE** are unknown (see **Special Precautions**).

DOSAGE AND DIRECTIONS FOR USE:

Recommended dosage in adults:

CIPLA-ZIDOVUDINE 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 $I0^9$/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.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

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 prior 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 (see **DOSAGE AND DIRECTIONS FOR USE**). 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 (see **INTERACTIONS**).

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 characterise 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 mmol/L: monitor regularly, and be alert for clinical signs.
- Lactate 5-10 mmol/L without symptoms: monitor closely.
- Lactate 5-10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate > 10 mmol/L: STOP all therapy (80% mortality in case studies).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms or signs such as fatigue, headache, vomiting, and reports of haematological disturbances, have been identified following acute over-dosage with zidovudine. Reported blood levels of zidovudine over 16 times the normal therapeutic level did not present with any short-term clinical, biochemical, or haematological sequelae in the patient.

Haemodialysis appears to have a limited effect on elimination of zidovudine but enhances the elimination of the inactive glucuronide metabolite.

TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

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.

STORAGE INSTRUCTIONS:

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

KEEP OUT OF REACH OF CHILDREN

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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