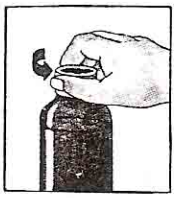
PATIENT INFORMATION FOR ZIDOVIR ORAL SOLUTION

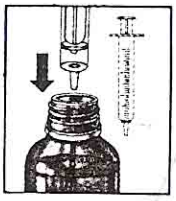
To facilitate accurate dosing, **Zidovir** liquid is supplied along with a syringe. Remember each millilitre (ml) of the liquid is equivalent to 10 mg of the drug.

MEASURING THE REQUIRED DOSE USING THE SYRINGE:

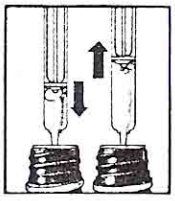


1. Remove the cap.

2. Introduce the cannula completely into the bottle till the white cap reaches the mouth of the bottle.



3. Remove the plastic case of the syringe. Insert the syringe into the white cap of the cannula.



4. Draw the required volume of liquid (as prescribed by the doctor) into the syringe ensuring that no large bubbles are present in the syringe. Presence of a few minute bubbles will not adversely affect the dosage.

5. Administer the dose into mouth by pushing syringe plunger. Swallow the liquid. Rinse the syringe with clean water.

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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Zidovir

Composition
Zidovudine Oral Solution USP
Zidovir
Each 5 ml contains
Zidovudine USP.....50 mg

Zidovudine Capsules USP
Zidovir-100
Each capsule contains
Zidovudine USP..... 100 mg

Zidovudine Tablets
Zidovir-300
Each film-coated tablet contains
Zidovudine USP .....300 mg
Colour: Titanium Dioxide IP

Description
Zidovudine, a thymidine analogue, is an antiretroviral drug active against human immunodeficiency virus (HIV). Cellular thymidine kinase converts zidovudine into zidovudine monophosphate and further to the diphosphate. Zidovudine diphosphate is converted to the triphosphate derivative by other cellular enzymes. Zidovudine triphosphate interferes with the HIV viral RNA dependent DNA polymerase (reverse transcriptase), and thus inhibits viral replication. Zidovudine triphosphate also inhibits cellular α - DNA polymerase at concentrations 100-fold higher than those required to inhibit reverse transcriptase. In vitro, reverse transcriptase incorporates zidovudine triphosphate into the growing chain of DNA, and the DNA chain is terminated.

Indications
Zidovir is indicated for the treatment of HIV infection when antiretroviral therapy is warranted.
The duration of clinical benefit from antiretroviral therapy may be limited. Alterations in antiretroviral therapy should be considered if disease progression occurs during treatment.

Maternal-Fetal HIV Transmission
Zidovir is also indicated for the prevention of maternal-fetal HIV transmission. The efficacy of this regimen for preventing HIV transmission in women who have received zidovudine for a long period before pregnancy has not been evaluated. The safety of zidovudine for the mother or foetus during the first trimester of pregnancy has not been assessed.

Dosage and Administration
The recommended total oral daily dose of **Zidovir** is 600 mg per day in divided doses in combination with other antiretroviral agents and 500 mg (100 mg every 4 hours while awake) or 600 mg per day in divided doses for monotherapy. The effectiveness of this dose compared to higher dosing regimens in improving the neurologic dysfunction associated with HIV disease is unknown. A small randomized study found a greater effect of higher doses of zidovudine on improvement of neurological symptoms in patients with pre-existing neurological disease.
Paediatrics: The recommended dose in children 3 months to 12 years of age is 180 mg/m^2 every 6 hours (720 mg/m^2 per day), not to exceed 200 mg every 6 hours.
Maternal-Fetal HIV Transmission : Zidovudine is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral zidovudine beginning between 14 and 34 weeks of gestation, intravenous zidovudine during labour, and administration of zidovudine syrup to the neonate after birth. The recommended dosing regimen for administration to pregnant women (> 14 weeks of pregnancy) and their neonates is:

Maternal dosing : 100 mg orally 5 times per day until the start of labour. During labour and delivery, intravenous zidovudine should be administered at 2 mg/kg (total body weight) until clamping of the umbilical cord.

Neonatal dosing : 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered zidovudine intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. (See *Warnings and Precautions* if hepatic disease or renal insufficiency is present).

Patient Monitoring
Haematologic toxicities appear to be related to pre-treatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to

detect serious anaemia or granulocytopenia (See *Warnings and Precautions*). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks.

Dose adjustment : Significant anaemia (hemoglobin of < 7.5 g/dL or reduction of > 25% of baseline) and/or significant granulocytopenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (See *Warnings and Precautions*). For less severe anaemia or neutropenia, a reduction in daily dose may be adequate. In patients who develop significant anaemia, dose modification does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose modification, gradual increases in dose may be appropriate depending on hematologic indices and patient tolerance.
In end-stage renal disease patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours.
There are insufficient data to recommend dosage adjustment of **Zidovir** in patients with impaired hepatic function.

Contraindications
Zidovir capsules, ~~tablets and syrup are~~ is contraindicated for patients who exhibit potentially life-threatening allergic reactions to any of the components of the formulation. However, significant anaemia, in many cases requiring dose adjustment, discontinuation of zidovudine, and/or blood transfusions has occurred during treatment with zidovudine alone or in combination with other antiretrovirals.

Warnings and Precautions
Before combination therapy with **Zidovir** is initiated, consult the complete prescribing information for each drug. The safety profile of **Zidovir** plus other antiretroviral agents reflects the individual safety profiles of each component.
The incidence of adverse reactions appears to increase with disease progression, and patients should be monitored carefully, especially as disease progression occurs.

Bone Marrow Suppression

Zidovir should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count < 1000 cells/mm^3 or hemoglobin < 9.5 g/dL. There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug.
Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with zidovudine. For patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anaemia or neutropenia develops, dosage adjustments may be necessary (See *Dosage and Administration*).

Myopathy
Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of zidovudine.

Lactic acidosis/severe hepatomegaly with steatosis
Rare occurrences of potentially fatal lactic acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported with the use of certain antiretroviral nucleoside analogues. Lactic acidosis should be considered whenever a patient receiving therapy with zidovudine develops unexplained tachypnea, dyspnea or fall in serum bicarbonate level. Under these circumstances, therapy with **Zidovir** should be suspended until the diagnosis of lactic acidosis has been excluded. Caution should be exercised when administering **Zidovir** to any patient, particularly obese women, with hepatomegaly, hepatitis, or other known risk factor for liver disease. Treatment with zidovudine should be suspended in the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly, or metabolic/lactic acidosis of unknown etiology.

Other serious adverse reactions
Reports of pancreatitis, sensitization reactions, vasculitis and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. Changes in skin and nail pigmentation have been associated with the use of zidovudine.

Drug Interactions
Ganciclovir, interferon alpha : Use of zidovudine in combination with either ganciclovir or interferon alpha increases the risk of hematologic toxicities. Hematologic parameters should be monitored frequently in all patients receiving either of these combinations.
Bone Marrow Suppressive Agents/Cytotoxic Agents : Co-administration of zidovudine with drugs that are cytotoxic or which interfere with RBC/WBC number or function (eg. dapsone, flucytosine, vincristine, vinblastine or adriamycin) may increase the risk of hematologic toxicity.
Probenecid : Limited data suggest that probenecid may increase zidovudine levels by inhibiting glucuronidation and/or by reducing renal excretion of zidovudine.
Phenytoin : Phenytoin plamsa levels have been reported to be low in some patients receiving zidovudine. In one study, a 30% decrease in oral zidovudine clearance was observed with phenytoin.
Methadone : No adjustments in methadone-maintenance requirements were reported in a study of nine HIV-positive patients receiving methadone maintenance.
Fluconazole : The co-administration of fluconazole with zidovudine has been reported to interfere with the oral clearance and metabolism of zidovudine.
Atovaquone : A decrease in zidovudine oral clearance was observed.
Valproic Acid : Data suggest that valproic acid increases the oral bioavailability of zidovudine through inhibition of first-pass hepatic metabolism. Patients should be monitored for a possible increase in zidovudine-related adverse events.
Lamivudine : Co-administration of zidovudine with lamivudine resulted in an increase in the maximum concentration (C_{max}) of zidovudine.
Other nucleoside analogues : Experimental nucleoside analogues affecting DNA replication such as ribavirin antagonize the antiviral activity of zidovudine against HIV.

Pregnancy
Congenital abnormalities were found to occur with similar frequency between infants born to mothers who received zidovudine and infants born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognised on ultrasound before or immediately after initiation of study drugs.

Nursing Mothers
HIV-infected women are advised not to breast-feed to avoid postnatal transmission of HIV to a child who may not yet be infected. Zidovudine is excreted in human milk.

Impaired Renal and Hepatic Function
In end-stage renal disease patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours. There are insufficient data to recommend dose adjustment of **Zidovir** in patients with impaired hepatic function.

Side Effects

Monotherapy
Adults
The frequency and severity of adverse events associated with the use of zidovudine in adults are greater in patients with more advanced infection at the time of initiation of therapy.
The anaemia reported in patients with advanced HIV disease receiving zidovudine appeared to be the result of impaired erythrocyte maturation. Thrombocytopenia has also been reported in patients with advanced disease. Mild drug-associated elevations in total bilirubin levels have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection.
Clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1,500 mg/day of zidovudine were : fever, headache, nausea, vomiting, anorexia, myalgia, insomnia, dizziness, paraesthesia, dyspnoea and rash. Malaise, gastrointestinal pain, dyspepsia, and taste perversion were also reported.

Paediatrics
Anaemia and granulocytopenia among paediatric patients with advanced HIV disease receiving zidovudine occurred with similar incidence to that reported for adults with AIDS or advanced AIDS-related complex. Macrocytosis was frequently observed.
Other adverse events were similar to that observed in adults.

Use for the prevention of Maternal-Fetal Transmission
The most commonly reported adverse experiences were anaemia and neutropenia. No neonates with anaemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with zidovudine.

Overdosage
No reported cases of acute overdosage (up to 50 gms) in both children and adults have been fatal. The consistent finding in these cases was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not severe. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine while elimination of its primary metabolite is enhanced.

Presentation

~~**Zidovir Oral Solution**~~	~~Bottle of 100 ml~~
Zidovir-100 Capsules	~~Blister pack of 10 Capsules and~~ Container of 100 Capsules
Zidovir-300 Tablets	~~Blister pack of 10 Tablets and~~ Container of 60 Tablets