1.3 PRESCRIBING INFORMATION

1.3.1 Summary of Product Characteristics

Enclosed overleaf.

SUMMARY OF PRODUCT CHARACTERISTICS

Zidovudine Oral Solution USP 50 mg/5ml
R_X Only

1 NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Zidovudine Oral Solution USP 50 mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral solution contains Zidovudine USP 50 mg

Excipients: Sucrose, glycerin, citric acid, sodium benzoate, strawberry flavor and purified water.

3 PHARMACEUTICAL FORM

Colorless to pale yellow strawberry flavoured syrup. Zidovudine oral solution comes in bottles of 240 ml.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zidovudine oral solution is indicated in anti-retroviral combination therapy for Human Immunodeficiency Virus (HIV) infected adults and children.

Zidovudine oral solution chemoprophylaxis is indicated for use in HIV-positive pregnant women (over 14 weeks of gestation) for prevention of maternal-foetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants.

4.2 Posology and method of administration

Dosage in adults:
The usual recommended dose of zidovudine oral solution in combination with other anti-retroviral agents is 500 or 600 mg/day in two or three divided dose.

Dosage in children:
3 months - 12 years:
The recommended dose of zidovudine oral solution is 360 to 480 mg/m^2 per day, in 3 or 4 divided doses in combination with other antiretroviral agents. The maximum dosage should not exceed 200 mg every 6 hours.

<3 months:
The limited data available are insufficient to propose specific dosage recommendations (See below -maternal foetal transmission and 5.2 Pharmacokinetic properties).

Dosage in the prevention of maternal-foetal transmission:
Although the optimal dosage schedule has not been identified the following dosage regimen has been shown to be effective. Pregnant women (over 14 weeks of gestation) should be given 500 mg/day orally (100 mg five times per day) until the beginning of labour. During labour and delivery zidovudine should be administered intravenously at 2 mg/kg bodyweight

given over one hour followed by a continuous intravenous infusion at 1 mg/kg/h until the umbilical cord is clamped.

The newborn infants should be given 2 mg/kg bodyweight orally every 6 hours starting within 12 hours after birth and continuing until 6 weeks old (e.g. a 3 kg neonate would require a 0.6 ml dose of oral solution every 6 hours).

Due to the small volumes of oral solution required, care should be taken when calculating neonate doses. To facilitate dosing precision a 1 ml syringe is included in the neonate pack.
Infants unable to receive oral dosing should be given zidovudine intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours. In case of planned caesarean, the infusion should be started 4 hours before the operation. In the event of a false labour, the zidovudine infusion should be stopped and oral dosing restarted.

Dosage adjustments in patients with haematological adverse reactions:
Dosage reduction or interruption of zidovudine oral soloution 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 (see 4.3 Contraindications and 4.4 Special warnings and precautions for use)

Dosage in the elderly:
Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. However, since special care is advised in this age group due to age-associated changes such as the decrease in renal function and alterations in haematological parameters, appropriate monitoring of patients before and during use of zidovudine oral solution is advised.

Dosage in renal impairment:
In patients with severe renal impairment, apparent zidovudine clearance after oral zidovudine administration was approximately 50% of that reported in healthy subjects with normal renal function. Therefore a dosage reduction to 300-400mg daily is recommended for patients with severe renal impairment with creatinine clearance -$\leq$ 10ml/min. Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. Haemodialysis and peritoneal dialysis have no significant effect on zidovudine elimination whereas elimination of the glucuronide metabolite is increased.

Dosage in hepatic impairment:
Data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Dosage reductions may be necessary but, as there is only limited data available, precise recommendations cannot be made. If monitoring of plasma zidovudine levels is not feasible, physicians will need to monitor for signs of intolerance, such as the development of haematological adverse reactions (anaemia, leucopenia, neutropenia) and reduce the dose and/or increase the interval between doses as appropriate.

4.3 Contraindications:

Zidovudine is contraindicated in patients with clinically significant hypersensitivity to zidovudine or to any of the excipients.

Zidovudine is contraindicated in patients with abnormally low neutrophil counts (< 0.75 × 10^6/l) or low haemoglobin (< 7.5 g/dl or 4.7 mmol/l).

Zidovudine is contraindicated in newborn infants with hyperbilirubinaemia requiring treatment other than phototherapy, or with transaminase levels of over five times the upper limit of normal.

4.4 Special warnings and precautions for use

Transmission of HIV
Treatment with Zidovudine Oral Solution 50 mg/5 ml has not been shown to eliminate the risk of transmission of HIV infection by sexual contact or by blood transfer, although the risk may be reduced. Patients should continue to use appropriate precautions to prevent transmission of HIV.

Other drugs
The concomitant use of rifampicin or stavudine with zidovudine should be avoided (see section 4.5).

Haematological Adverse Reactions
Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can occur in patients receiving zidovudine. These are dose dependent and usually occur after 4 to 6 weeks of therapy. Discontinuation of zidovudine may be required if severe anaemia (< 9 g/dl (5.6 mmol/l)) or myelosuppression (neutrophil count < 1.0 × 10^9/l) occurs during treatment with zidovudine.

Liver disease
Caution should be exercised when administering nucleoside reverse transcriptase inhibitors (NRTIs), including zidovudine, to any patient with liver disease.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please also refer to the relevant product information for these medicinal products.

Patients co-infected with hepatitis C virus: The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

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 according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Immune reconstitution syndrome
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Lactic acidosis
Lactic acidosis is a rare but severe, potentially life-threatening complication associated with nucleoside reverse transcriptase inhibitor (NRTI) use. It may occur after a few to several months of treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI-related lactic acidosis include female gender and obesity; patients with hepatitis C and treated with interferon alfa and ribavirin may be at special risk. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs, including zidovudine. Lactic acid levels > 10 mmol/l usually are a medical emergency.

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 postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late- onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour).

Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Lipodystrophy
Combination antiretroviral therapy has been associated with a redistribution of body fat (lipodystrophy) in HIV patients. A higher risk of peripheral fat loss has been associated with stavudine or zidovudine use, and also with e.g. older age of the patient, longer duration of ART and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8). Lipid disorders should be managed appropriately, including the substitution of zidovudine by an alternative antiretroviral agent, if feasible (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction:

Limited data suggests that co-administration of zidovudine with rifampicin decreases the AUC (area under the plasma concentration curve) of zidovudine by 48% ± 34%. This may result in a partial loss or total loss of efficacy of zidovudine. The concomitant use of rifampicin with zidovudine should be avoided (see section 4.4).

Zidovudine in combination with stavudine is antagonistic in vitro. The concomitant use of stavudine with zidovudine should be avoided (see section 4.4).

Probenecid increases the AUC of zidovudine by 106% (range 100 to 170%). Patients receiving both drugs should be closely monitored for haematological toxicity.

A modest increase in C_{max} (28%) was observed for zidovudine when administered with lamivudine, but overall exposure (AUC) was not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while in one patient a high level was noted. These observations suggest that phenytoin levels should be carefully monitored in patients receiving both drugs.

Atovaquone: zidovudine does not appear to affect the pharmacokinetics of atovaquone. However, pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a three week, concomitant course of atovaquone for the treatment of acute PCP would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.

Valproic acid, fluconazole or methadone when co-administered with zidovudine have been shown to increase the AUC with a corresponding decrease in its clearance. As only limited data are available the clinical significance of these findings is unclear but if zidovudine is used concurrently with either valproic acid, fluconazole or methadone, patients should be monitored closely for potential toxicity of zidovudine.

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 elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination antiretroviral regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive drugs (eg. systemic pentamidine, dapsone, pyrimethamine, sulfamethoxazole + trimethoprim, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with any of these drugs is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.

Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with sulfamethoxazole + trimethoprim, aerosolised pentamidine, pyrimethamine and aciclovir at doses used in prophylaxis of opportunistic infections.

Clarithromycin tablets reduce the absorption of zidovudine. This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.

4.6 Pregnancy and lactation

Pregnancy:

A large amount of data on pregnant women indicate no malformative nor feto/neonatal toxitcity. Retrovir can be used during pregnancy if clinically needed. Studies in pregnant rats and rabbits given zidovudine orally at dosage levels up to 450 and 500 mg/kg/day

respectively during the major period of organogenesis have revealed no evidence of teratogenicity. There was, however, a statistically significant increase in foetal resorptions in rats given 150 to 450 mg/kg/day and in rabbits given 500 mg/kg/day.

A risks to the fetus cannot be ruled out.

Fertility
Zidovudine did not impair male or female fertility in rats given oral doses of up to 450 mg/kg/day. There are no data on the effect of zidovudine on human female fertility. In men, zidovudine has not been shown to affect sperm count, morphology or motility.

Breastfeeding
Zidovudine is excreted into the breast milk of lactating mothers. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. The clinical status of the patient and the adverse reaction profile of Zidovudine Oral Solution USP 50 mg/5ml should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects:

The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia. These occurred more frequently at higher doses (1.2–1.5 g/day) and with advanced HIV disease, particularly in patients with CD4 cell counts less than 100/ml. Dosage reduction or cessation of therapy may become necessary (see section 4.4).

Also, zidovudine has been associated with lipodystrophy syndrome, including peripheral fat loss (see section 4.4).

The adverse reaction profile appears similar for adults and children.

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV-1 infection with zidovudine.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10 000, < 1/1000), very rare (<1/10 000), or not known (cannot be estimated from the available data).

<u>Blood and lymphatic systems disorders</u>
Common: anaemia, leucopenia, and neutropenia

Uncommon: thrombocytopenia and ancytopenia
Rare: pure red cell anaemia
Very rare: aplastic anaemia

<u>Metabolic and nutrition disorders</u>
Rare: lactic acidosis
Not known: changes in distribution of body fat, insulin resistance, hyperglycaemia, hyperlipidaemia, hyperlactataemia (see section 4.4)

Psychiatric disorders
Rare: anxiety and depression

Nervous system disorders
Very common: headache
Common: dizziness
Rare: insomnia, loss of mental acuity, somnolence, paraesthesia, convulsions

Cardiac disorders
Rare: cardiomyopathy

Respiratory disorders
Uncommon: dyspnoea
Rare: cough

Gastrointestinal disorders
Very common: nausea
Common: vomiting, diarrhoea, abdominal pain
Uncommon: flatulence
Rare: pancreatitis, oral mucosa pigmentation, taste disturbance, dyspepsia

Hepatobiliary disorders
Common: transient elevation of liver enzymes and bilirubin
Rare: severe hepatomegaly with steatosis

Reproductive system and breast disorders
Rare: gynaecomastia

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus
Rare: nail and skin pigmentation, urticaria, sweating

Musculoskeletal and connective tissue disorders
Common: myalgia
Uncommon: myopathy
Not known: osteonecrosis (see section 4.4)

General disorders and administration-site conditions
Common: malaise
Uncommon: asthenia, fever, generalised pain
Rare: chest pain, influenza-like syndrome, chills
Not known: immune reconstitution syndrome (see section 4.4)

Renal and urinary disorders
Rare: urinary frequency increased

Adverse reactions with zidovudine for the prevention of maternal-foetal transmission:
Haemoglobin concentrations in infants directly exposed to zidovudine for six weeks postpartum were marginally lower than in infants in the placebo group, but transfusion was not required. Anaemia resolved within 6 weeks after completion of zidovudine therapy.

4.9 Overdose

Symptoms and signs:

Acute overdoses of zidovudine have been reported. These involved exposures up to 50 g. No specific symptoms or signs have been identified following overdosage apart from those listed as adverse events. All recovered without permanent sequelae.

Treatment:
Patients should be observed closely for evidence of toxicity (see section 4.8) and given the necessary supportive therapy. Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiretroviral for systemic use, nucleoside reverse transcriptase inhibitors, ATC code: J05AF01

Zidovudine is a thymidine dideoxynucleoside analogue that has activity against HIV-1 and HIV-2. Zidovudine is phosphorylated by thymidine kinase to the active metabolite zidovudine 5'-triphosphate. Its mechanism of action is as a chain terminator of viral reverse transcription.

In addition to the inhibitory effect on HIV reverse transcriptase, zidovudine 5'-triphosphate inhibits cellular DNA polymerase beta and gamma and has been shown to reduce the synthesis of mitochondrial DNA.

Clinical efficacy
Zidovudine has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs. These studies have demonstrated significant decreases in plasma HIV RNA and increases in CD4-cell counts when used in combination with another nucleoside reverse transcriptase inhibitor (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). In recent studies in treatment-naïve patients infected with HIV-1, by intention-to-treat analysis > 75% of subjects have plasma HIV RNA < 50 copies/ml after 48 weeks of combination antiretroviral treatment including zidovudine.

In the US ACTG 076 trial, zidovudine reduced the rate of maternal–fetal transmission of HIV-1 (23% infection rate for placebo versus 8% for zidovudine) when HIV-positive pregnant women (14 to 34 weeks gestation) were given 100 mg five times a day and their newborn infants were given 2 mg/kg every 6 hours until 6 weeks of age. In the shorter duration 1998 Thailand CDC study, use of oral zidovudine therapy only (300 mg twice daily), from week 36 of pregnancy until delivery, also reduced the rate of maternal-foetal transmission of HIV (19% infection rate for placebo versus 9% for zidovudine).

Viral resistance
On virological failure, resistance to zidovudine is developed along two separate, though not mutually exclusive, pathways. The first of these include M41L, L210W and T215F/Y. The second includes D67N, K70R and K219E/Q. Collectively these mutations are termed “thymidine analogue mutations” (TAM). In viruses with M184V, two to three TAMs are generally required for phenotypically detectable and clinically significant zidovudine resistance. M41L, L210W, and T215Y have a greater effect on zidovudine susceptibility and cross- resistance to other NRTIs than the other TAMs. Other important mutations selected for by zidovudine include T69 insertion mutations and the Q151M complex, where this mutation appears in combination with mutations at positions 75, 77, and 116. Both of these patterns confer high-level resistance to zidovudine and all other presently available NRTIs. The likelihood of a gradual accumulation of mutations conferring resistance to the entire class of NRTI, upon virological failure with combination therapy including zidovudine, underscores the importance of early detection of virological failure. Delayed detection of virological failure may severely limit the options for second line therapy.

5.2 Pharmacokinetic properties

Pharmacokinetics in adults:

Absorption

No pharmacokinetic data are available for Zidovudine Oral Solution USP 50 mg/5ml as it is regarded as qualitatively and with respect to the ratio of active and other ingredients essentially the same as the innovator product Retrovir 10 mg/ml oral solution (GSK).

Distribution

The mean apparent volume of distribution of zidovudine is 1.6 l/kg. Plasma protein binding is 34–38%.

Metabolism

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50–80% of the administered dose eliminated by renal excretion. 3'-amino-3'- deoxythymidine has been identified as a metabolite of zidovudine following intravenous dosing.

Elimination

In studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 l/hour/kg. The half-life of intracellular zidovudine triphosphate has been estimated to around 7 hours. Renal clearance of zidovudine is estimated to be 0.34 l/hour/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

Paediatric population:

Absorption

In children over the age of 5–6 months, the pharmacokinetic profile of zidovudine is similar to that in adults.

Distribution

With intravenous dosing, the mean terminal plasma half-life and total body clearance were 1.5 hours and 30.9 ml/minute/kg respectively.

In children the mean cerebrospinal fluid/plasma zidovudine concentration ratio ranged from 0.52–0.85, as determined during oral therapy 0.5 to 4 hours after dosing and was 0.87 as determined during intravenous therapy 1–5 hours after a 1-hour infusion. During continuous intravenous infusion, the mean steady-state cerebrospinal fluid/plasma concentration ratio was 0.24.

Metabolism

The major metabolite is 5'-glucuronide. After intravenous dosing, 29% of the dose was recovered unchanged in the urine and 45% excreted as the glucuronide.

Excretion

Renal clearance of zidovudine greatly exceeds creatinine clearance indicating that significant tubular secretion takes place.

The data available on the pharmacokinetics in neonates and young infants indicate that glucuronidation of zidovudine is reduced with a consequent increase in bioavailability, reduction in clearance and longer half-life in infants less than 14 days old but thereafter the pharmacokinetics appear similar to those reported in adults.

5.3 Preclinical safety data

Administration of zidovudine in animal toxicity studies at high doses was not associated with any major organ toxicity.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, glycerin, citric acid, sodium benzoate, strawberry flavor and purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Please refer outer package for expiry date.

6.4 Special precautions for storage

Store below 30ºC. Keep the bottle tightly closed. Store the bottle in the original outer carton.

6.5 Nature and contents of container

White opaque high density polyethylene bottle, containing 240 ml of oral solution, with a plastic cap and polyethylene wad.

An oral-dosing syringe is included in the pack, with an adaptor, which should be fitted to the bottle before use.

6.6 Instructions for use and handling

An oral dosing syringe along with cannula is provided.

7 MARKETING AUTHORIZATION HOLDER:

AUROBINDO

M/s Aurobindo Pharma Ltd.,
Plot No.: 2, Maitrivihar
Ameerpet, Hyderabad-500 038
India.

8 DATE OF REVISION OF THE TEXT: 11.07.2018

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Botswana Reg. No.: BOT 0700905 S2
NAFDAC Reg. No.: 04-8376
Tanzania Reg. No.: Tan 06, 248 J05A AUR
Zambia Reg. No.: 127/033

POM

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

Zidovudine Oral Solution USP 50 mg/5 ml

$R_{X\ Only}$

Read all of this leaflet carefully before your child starts taking this medicine.

- Keep this leaflet; you may need to read it again.
- If you have any further questions, please ask the doctor, health care provider or pharmacist.
- This medicine has been prescribed for your child. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell the doctor, health care provider or pharmacist.

In this leaflet:

Zidovudine Oral Solution USP 50mg/5ml

Zidovudine oral solution is a colorless to pale yellow, strawberry-flavoured, liquid containing 50 mg of the active ingredient zidovudine per 5 ml. Zidovudine oral solution also contains some inactive ingredients. These are sucrose, glycerin, citric acid, sodium benzoate, strawberry flavor and purified water.

Zidovudine oral solution comes in bottles of 240 ml.

The Marketing Authorisation Holder for Zidovudine oral solution is:

M/s Aurobindo Pharma Ltd

Plot No.: 2, Maitrivihar

Ameerpet, Hyderabad-500 038

India.

Zidovudine oral solution is manufactured by:

M/s Aurobindo Pharma Limited

Unit III, Sy. No. 313 & 314,

Bachupally, Bachupally Mandal,

Medchal-Malkajgiri District,

Telangana State, India.

1. **What is Zidovudine oral solution USP and what it is used for?**

Zidovudine Oral Solution USP 50 mg/5 ml, which contains zidovudine as the active ingredient, belongs to a group of antiviral medicines called *nucleoside analogue reverse transcriptase inhibitors* (NRTIs). These are used to treat human immunodeficiency virus (HIV) infection.

Zidovudine Oral Solution USP 50 mg/5 ml is used:

- in antiretroviral combination therapy for the treatment of HIV infection in children
- in newborns and infants, for the prevention of mother-to-child ransmission of HIV.

In therapy, zidovudine reduces the amount of virus in your child's body, and keeps it at a low level. It also increases *CD4 cell counts*. CD4 cells are a type of white blood cells that are important to help fight infection. The doctor or health care provider will be monitoring the effectiveness of your child's treatment.

Zidovudine Oral Solution 50 mg/5 ml may improve your child's condition, but it is not a cure for HIV infection. HIV infection is a disease spread by contact with blood (for example, by sharing injection needles) or by sexual contact with an infected individual.

Treatment with Zidovudine Oral Solution 50 mg/5 ml has not been shown to eliminate the risk of passing HIV infection on to others by sexual contact or by blood transfer. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

2. Questions you should ask yourself before taking Zidovudine oral solution.

Do not use Zidovudine Oral Solution if your child:

- Is allergic (*hypersensitive*) to zidovudine or to any of the other ingredients (see section 6,What Zidovudine 50 mg /5 ml Oral Solution contains);

- Has a very low red blood cell count (severe *anaemia*) or very low white blood cell count (*neutropenia*).

Do not use Zidovudine Oral Solution if a newborn baby has certain liver problems:

- Some cases of increased amount of bilirubin in the blood (*hyperbilirubinaemia*), a condition which might make the baby's skin look yellow;
- Excessive amount of certain liver enzymes in the blood

Take special care with Zidovudine Oral Solution

Before using this medicine, you should tell your doctor or health care provider if your child:

- suffers from liver disease (such as hepatitis) or severe kidney disease,

Blood disorders

Anaemia (low red blood cell count) and neutropenia/leucopenia (low white blood cell count) may occur within 4–6 weeks after starting treatment with Zidovudine Oral Solution USP 50 mg/5 ml. If severe, the physician or health care provider may stop treatment with Zidovudine Oral Solution USP 50 mg/5 ml. This occurs more commonly in patients with advanced HIV disease and with higher doses of zidovudine. Regular blood tests will be arranged to check whether there is a problem. This adverse reaction is infrequent in patients with early HIV disease and blood tests may be performed less frequently.

Lactic acidosis

The class of medicines to which Zidovudine Oral Solution USP 50 mg/5 ml belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Lactic acidosis is a build up of lactic acid in the body, which can cause dehydration and coma. Deep, rapid breathing, drowsiness, and non-specific symptoms such as nausea, vomiting and stomach pain, may indicate the development of lactic acidosis. In addition lactic acidosis may lead to rare cases of liver failure, renal failure or fatal hepatitis. This rare, but serious side effect occurs more often in women, particularly if very overweight. If your child has liver disease he or she may also be more at risk of getting this condition. While taking Zidovudine Oral Solution USP 50 mg/5 ml, the doctor or health care provider will monitor your child closely for any signs that he or she may be developing lactic acidosis.

Liver disease

Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for monitoring of liver function.

In patients with a chronic hepatitis B infection the treatment should not be stopped without instructions from the doctor or health care provider, as he or she may have a recurrence of the hepatitis. This recurrence may be more severe if the patient has serious liver disease.

Reactivation of immune system

People with advanced HIV infection (AIDS) have a weak immune system and are more likely to pick up serious infections (*opportunistic infection*). On starting treatment with antiviral medicines against HIV, old, hidden infections flare up causing signs and symptoms of inflammation. The inflammation may mark a return of the body's ability to fight off infection and is called *immune reconstitution syndrome*. If you notice any symptoms of infection in your child, please tell the doctor or health care provider immediately.

Fat distribution

Loss of body fat may occur in patients receiving zidovudine. Contact the doctor or health care provider if you notice changes in your child's body fat.

Bone problems
Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue). The risk of developing this disease may be higher if the immune system is severely weakened, or if one drinks alcohol regularly. So far, this disease has been reported mainly in adults. However, if your child suffers from joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement, inform the doctor or health care provider.

Other
Your child will need to take Zidovudine Oral Solution 50 mg/5 ml every day. This medicine helps to control your child's condition, but it is not a cure for HIV infection. Your child may continue to develop other infections (*opportunistic infection*) and other illnesses associated with HIV disease. You should keep in regular contact with your child's doctor or health care provider. Do not stop your child's medicine without first talking to the doctor or health care provider.

Taking other medicines

Please tell the doctor, health care provider or pharmacist if your child is taking or has recently taken any other medicines, including herbal medicines and medicines obtained without a prescription. These may affect the action of zidovudine, or zidovudine may affect their action.

Zidovudine Oral Solution 50 mg/5 ml should not be taken with either stavudine or ribavirin.

Zidovudine Oral Solution 50 mg/5 ml may also interact with valproic acid, fluconazole, methadone and probenecid making side effects worse; their use should be carefully considered.

Taking Zidovudine Oral Solution 50 mg/5 ml at the same time as other medicines that are potentially toxic to the kidneys or bone marrow may increase the risk of adverse reactions to Zidovudine Oral Solution 50 mg/5 ml. Such medicines include, for instance, pentamidine, dapsone, pyrimethamine, sulfamethoxazole + trimethoprim, amphotericin, flucytosine, ganciclovir, valganciclovir, interferon, vincristine, vinblastine and doxorubicin. If your child requires any of these medications with Zidovudine Oral Solution 50 mg/5 ml then the doctor may need to monitor his or her kidney function and blood parameters more closely and, if required, the dosage of one or more of the drugs may be reduced.

Taking Zidovudine Oral Solution 50 mg/5 ml with food and drink

Zidovudine Oral Solution 50 mg/5 ml may be taken with or without food.

Pregnancy

If a woman becomes pregnant, or is planning to become pregnant, she should contact the doctor or health care provider to discuss the potential adverse effects and the benefits and risks of the antiretroviral therapy to the pregnant woman and her child.

Breastfeeding
Zidovudine, the active ingredient in this medicine, is found in human breast milk.
A woman with HIV who wants to breastfeed her baby should discuss the risks and benefits with her doctor or healthcare provider.

Driving and using machines

No studies on the effects of zidovudine on the ability to drive and use machines have been performed. However, one should take into account the state of the person's health and the possible side effects of zidovudine before one considers driving or using machines.

3. How to take Zidovudine Oral Solution

Oral use.

Dosage in adults:
The usual recommended dose of zidovudine oral solution in combination with other anti-retroviral agents is 500 or 600 mg/day in two or three divided dose.

Dosage in children:
3 months - 12 years:
The recommended dose of zidovudine oral solution is 360 to 480 mg/m^2 per day, in 3 or 4 divided doses in combination with other antiretroviral agents. The maximum dosage should not exceed 200 mg every 6 hours.

<3 months:
The limited data available are insufficient to propose specific dosage recommendations (See below -maternal foetal transmission and 5.2 Pharmacokinetic properties).

Dosage in the prevention of maternal-foetal transmission:
Although the optimal dosage schedule has not been identified the following dosage regimen has been shown to be effective. Pregnant women (over 14 weeks of gestation) should be given 500 mg/day orally (100 mg five times per day) until the beginning of labour. During labour and delivery zidovudine should be administered intravenously at 2 mg/kg bodyweight given over one hour followed by a continuous intravenous infusion at 1 mg/kg/h until the umbilical cord is clamped.
The newborn infants should be given 2 mg/kg bodyweight orally every 6 hours starting within 12 hours after birth and continuing until 6 weeks old (e.g. a 3 kg neonate would require a 0.6 ml dose of oral solution every 6 hours).
Due to the small volumes of oral solution required, care should be taken when calculating neonate doses. To facilitate dosing precision a 1 ml syringe is included in the neonate pack.
Infants unable to receive oral dosing should be given zidovudine intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours. In case of planned caesarean, the infusion should be started 4 hours before the operation. In the event of a false labour, the zidovudine infusion should be stopped and oral dosing restarted.

Dosage adjustments in patients with haematological adverse reactions:
Dosage reduction or interruption of zidovudine oral soloution 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 (see 4.3 Contraindications and 4.4 Special warnings and precautions for use)

Dosage in the elderly:
Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. However, since special care is advised in this age group due to age-associated changes such as the decrease in renal function and alterations in haematological parameters, appropriate monitoring of patients before and during use of zidovudine oral solution is advised.

Dosage in renal impairment:
In patients with severe renal impairment, apparent zidovudine clearance after oral zidovudine administration was approximately 50% of that reported in healthy subjects with normal renal function. Therefore a dosage reduction to 300-400mg daily is recommended for patients with severe renal impairment with creatinine clearance -$\leq$ 10ml/min. Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. Haemodialysis and peritoneal dialysis have no significant effect on zidovudine elimination whereas elimination of the glucuronide metabolite is increased.

Dosage in hepatic impairment:
Data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Dosage reductions may be necessary but, as there is only limited data available, precise recommendations cannot be made. If monitoring of plasma zidovudine levels is not feasible, physicians will need to monitor for signs of intolerance, such as the development of haematological adverse reactions (anaemia, leucopenia, neutropenia) and reduce the dose and/or increase the interval between doses as appropriate.

Instructions for use

Use the oral dosing syringe supplied with the pack to measure your child's dose accurately.

The solution contains 10 mg of zidovudine per 1 ml.

1. Remove the bottle cap. Keep it safely
2. Hold the bottle firmly. Push the plastic adapter into the neck of the bottle.
3. Insert the syringe firmly into the adapter.
4. Turn the bottle upside down.
5. Pull out syringe plunger until the syringe contains the first part of your full dose.
6. Turn the bottle the correct way up. Remove the syringe from the adapter.
7. Put the syringe into your child's mouth, placing the tip of the syringe against the inside of your child's cheek. Slowly push the plunger in, allowing time to swallow. Do not push too hard and squirt the liquid into the back of your child's throat or your child

may choke.

8. Take the syringe out of the bottle and wash it thoroughly in clean water. Let it dry completely before you use it again.

Close the bottle tightly with the cap, leaving the adaptor in place

If one takes more Zidovudine Oral Solution than one should

If your child has taken too much Zidovudine Oral Solution USP 50 mg/5 ml, or if someone accidentally swallows some, there is no immediate danger. However, you should contact the doctor, health care provider, or the nearest hospital emergency department for further advice.

If one forgets to take Zidovudine Oral Solution

If your child accidentally misses a dose and you notice within 6 hours after the missed dose, give the missed dose as soon as possible. Give the next dose as regularly scheduled. If you notice later than 6 hours after the missed dose, then only give the normal dose when the next dose is due. Do not give a double dose to make up for forgotten individual doses.

If you have any further questions on the use of this product, ask the doctor, health care provider or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zidovudine Oral Solution USP 50 mg/5 ml can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zidovudine Oral Solution USP 50 mg/5 ml, or those caused by any other medicines your child may be taking at the same time, or by the HIV disease. For this reason, it is important that you inform the doctor or health care provider of any change in your child's health.

The most serious adverse reactions include anaemia (low red blood cell count), and low white blood cell count. These are more common in patients with advanced HIV infection.

Anaemia has not been serious during Zidovudine Oral Solution USP 50 mg/5 ml use for prevention of mother-to-child transmission.

Furthermore, zidovudine may cause loss of body fat, particularly in the arms, legs and face.

Very commonly reported (greater than 1 in every 10 patients treated) side effects are headache and nausea.

Commonly reported (greater than 1 in every 100 patients treated) side effects are feeling dizzy, vomiting, diarrhoea, stomach pain, muscle aches, decreased red blood cells (anaemia), decreased white blood cells (leucopenia, neutropenia) and transient increase of liver enzymes and bilirubin in the blood.

The following side effects are *uncommon* (between 1 in 1000 and 1 in 100 patients treated): wind (flatulence), feeling breathless, skin rash, general aches and pains, weakness, fever,

decreased blood platelets (thrombocytopenia) or all blood cells (pancytopenia) and muscle tissue disorders (myopathy).

There are *rare* reports (between 1 in 10 000 to 1 in 1000 patients treated) of anxiety, depression, sleeplessness (insomnia), not being able to concentrate, feeling drowsy, tingling of the skin, ('pins and needles'), cough, loss of appetite, taste disturbance, indigestion, inflammation of the pancreas (*pancreatitis*), chest pain, disease of the heart muscle, fits (convulsions), nail and skin pigmentation, colour change on the inside of the mouth, hives, chills, sweating, enlarged breasts in men, fat accumulation in the liver, inability to produce new red blood cells (pure red cell anaemia) and increased urinary frequency.

5. STORING Zidovudine Oral Solution USP 50 mg/5 ml

Do not store above $30^{O}C$.

Do not use after the expiry date stated on the container.

Keep out of the reach and sight of children.

Do not use Zidovudine Oral Solution after the expiry date which is stated on the bottle. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Further information

For any information about this medicinal product please contact the local representative of the Marketing Authorization Holder.

"If you notice any side effect (s) with the use of this drug, please report it immediately via internet to the following e-mail address: pharmacovigilance@aurobindo.com