1.3 PRESCRIBING INFORMATION

1.3.2 Patient Information leaflet

Enclosed overleaf.

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