SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Zidovudine Oral Solution 50 mg/5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
5 ml of solution contains 50 mg zidovudine
5 ml of solution contains 2.16 g sucrose
For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM
Zidovudine oral solution
Colorless to pale-yellow strawberry-flavoured liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Zidovudine Oral Solution 50 mg/5 ml is indicated in antiretroviral combination therapy for human immunodeficiency virus (HIV) infected children.
Zidovudine Oral Solution 50 mg/5 ml is indicated for primary prophylaxis of HIV infection in newborn infants.
Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

4.2 Posology and method of administration
Oral use. Zidovudine may be taken with or without food.
Therapy should be prescribed by a physician experienced in the management of HIV-1 infection.

Instructions for use

The solution contains 10 mg of zidovudine per 1 ml.
The maximum dosage should not exceed 300 mg twice daily.

<table>
<thead>
<tr>
<th>Weight range (kg)</th>
<th>Dose</th>
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<tbody>
<tr>
<td>3 to 5.9 kg</td>
<td>6 ml (60 mg) twice daily</td>
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<tr>
<td>6 to 9.9 kg</td>
<td>9 ml (90 mg) twice daily</td>
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<tr>
<td>10 to 13.9 kg</td>
<td>12 ml (120 mg) twice daily</td>
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For patients weighing more than 14 kg other formulations containing higher amounts of the active substance are available

*Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
Dose for prevention of mother-to-child transmission (MTCT)

Start within 12 hours after birth and continue up to 6 weeks of age, depending on national recommendations.

| Recommended Dosing Based on Weight Bands for Children from birth to 6 weeks of age* |
|---------------------------------|---------------------------------|
| Birth weight 2000-2499 g        | 1 ml (10 mg) twice daily         |
| Birth weight above 2500 g       | 1.5 ml (15 mg) twice daily       |

*Low birth weight infants should receive mg/kg dosing. WHO suggests 4 mg/kg every 12 hours.

Due to the small volumes of oral solution required, care should be taken when calculating neonate doses.

**Dosage adjustments**

*Patients with haematological adverse reactions*
Substitution of zidovudine should be considered in patients whose haemoglobin level or neutrophil count fall to clinically significant levels. Other potential causes of anaemia or neutropenia should be excluded. Zidovudine dose reduction or interruption should be considered in the absence of alternative treatments (see sections 4.3 and 4.4).

*Liver Disease*
No dose adjustment is necessary for mild to moderate liver impairment but may be necessary for severe liver impairment.

*Renal Impairment*
In patients with severe renal failure (creatinine clearance < 10 ml/minute), with or without haemodialysis, the dose should be reduced. In adults, a 33 to 50% dose reduction of zidovudine is recommended.

### 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 × 10⁶/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 special 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 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 × 10⁹/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 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 pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

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).

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 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.
**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 Cmax (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.

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%).

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.

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*

No increased risk of birth defects has been reported for zidovudine ([www.apregistry.com](http://www.apregistry.com)). However, risks to the fetus cannot be ruled out.
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.

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.

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 50 mg/5 ml 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).

Blood and lymphatic systems disorders
Common: anaemia, leucopenia, and neutropenia
Uncommon: thrombocytopenia and pancytopenia
Rare: pure red cell anaemia
Very rare: aplastic anaemia.

Metabolic and nutrition disorders
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

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

Absorption

Zidovudine is well absorbed from the gastrointestinal tract, with a bioavailability of 60 – 70%. No pharmacokinetic data are available for Zidovudine Oral Solution 50 mg/5 ml.

Zidovudine Oral Solution 50 mg/5 ml has the same strength (100 mg/10 ml) and a composition essentially similar to that of the reference product, Retrovir® (GlaxoSmithKline). Moreover, evidence has been provided that the excipients have no effect on the absorption of zidovudine. Accordingly, Zidovudine (oral solution) is considered bioequivalent to Retrovir® 100 mg/10 ml oral solution. In children, steady-state Cmax level of zidovudine (innovator product) was 4.45 µM (1.19 µg/ml) after a dose of zidovudine (in solution) 120 mg/m² body surface area and 7.7 µM (2.06 µg/ml) after 180 mg/m². Dosages of 180 mg/m² four times daily in children produced similar systemic exposure (24 hour AUC 40.0 hour·µM or 10.7 hour·µg/ml) as doses of 200 mg six times daily in adults (40.7 hour·µM or 10.9 hour·µg/ml).

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
Anhydrous citric acid
Glycerol
Purified water
Sodium benzoate
Strawberry flavour
Sucrose

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months
6.4 Special precautions for storage
Do not store above 25° C

6.5 Nature and contents of container
A 250-ml high-density polyethylene (HDPE) bottle with child-resistant plastic cap (with either induction sealing (FSE) wad), containing 240 ml Zidovudine Oral Solution 50 mg/5 ml. It is accompanied by both 10-ml polypropylene oral dosing syringe and 1.5-ml dosing syringe for dosage measurement.

6.6 Instructions for use and handling and disposal
An oral dosing syringe along with cannula is provided.

The solution contains 10 mg of zidovudine per 1 ml.

1. The bottle cap should be removed and kept safely.
2. The cannula is inserted into the bottle, such that its cap fits into the mouth of the bottle.
3. The plastic case of the calibrated syringe is removed and the syringe inserted into the cannula.
4. The syringe is used to draw the required volume of the suspension (as prescribed by the doctor or health care provider) while ensuring that no large bubbles appear in the syringe.
5. The dose is then administered into the child’s mouth with tip of cannula against the child’s cheek, by slowly pushing the plunger, allowing time to swallow. Do not push too hard or squirt into the back of the throat, to avoid choking.
6. The syringe and cannula should be washed thoroughly in clean water and allowed to dry. It should be completely dry before re-use.
7. Close the bottle tightly with cap.

7. SUPPLIER
Hetero Labs Ltd
7-2-A2 Hetero Corporate
Industrial Estates
Sanath Nagar
Hyderabad 500 018
Andhra Pradesh
INDIA
Tel. + 91 40 23704923
Fax + 91 40 23704926
Email: contact@heterodrugs.com

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)
HA486

9. DATE OF FIRST PREQUALIFICATION
3 November 2011

10. DATE OF REVISION OF THE TEXT
References

This text is primarily based on the European SmPC for Zidovudine, available at:
http://www.medicines.org.uk/EMC/medicine/10419/SPC/Zidovudine+100+mg+10+ml%2c+oral+solutio
n/

Section 4.2
Dosage in children
Antiretroviral therapy for HIV infection in infants and children: Towards universal access;
Recommendations for a public health approach: 2010 revision:
Dosage in the prevention of maternal-foetal transmission
WHO: Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards
universal access Recommendations for a public health approach

Section 4.4
Lactic acidosis
A. Carr et al., AIDS 14, 1171 (2000).

Section 4.6
Breastfeeding
Guidelines on HIV and infant feeding 2010:

Section 4.8
(2005).
K. E. Squires et al., AIDS 14, 1591 (2000).

Section 5.1