

Zidovudine 100 mg Capsules  
Zidovudine 300 mg Tablets  
Zidovudine Oral Solution

## **ZIDOVIR**

**WARNINGS: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS.**

**ZIDOVUDINE HAS BEEN ASSOCIATED WITH HEMATOLOGICAL TOXICITY, INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV-1 DISEASE (SEE WARNINGS AND PRECAUTIONS).**

**PROLONGED USE OF ZIDOVUDINE HAS BEEN ASSOCIATED WITH SYMPTOMATIC MYOPATHY. (SEE WARNINGS AND PRECAUTIONS).**

**LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZIDOVUDINE AND OTHER ANTIRETROVIRALS. SUSPEND TREATMENT IF CLINICAL OR LABORATORY FINDINGS SUGGESTIVE OF LACTIC ACIDOSIS OR PRONOUNCED HEPATOTOXICITY OCCUR (SEE WARNINGS AND PRECAUTIONS).**

## **COMPOSITION**

### **ZIDOVIR-100 Capsules**

Each capsule contains:  
Zidovudine ... 100 mg

### **ZIDOVIR-300 Tablets**

Each tablet contains:  
Zidovudine ... 300 mg

### **ZIDOVIR Oral Solution**

Each 5 ml contains:  
Zidovudine ... 50 mg

## **DOSAGE FORM**

Capsule, tablet and solution

## **PHARMACOLOGY**

### **Pharmacodynamics**

Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide

analogue. ZDV-TP is a weak inhibitor of the cellular DNA polymerases  $\alpha$  and  $\gamma$  and has been reported to be incorporated into the DNA of cells in culture.

## Pharmacokinetics

### Adults

#### ***Absorption and Bioavailability***

In adults, following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hours. The AUC was equivalent when zidovudine was administered as Zidovudine Tablets or Syrup compared with Zidovudine Capsules. The pharmacokinetic properties of zidovudine in fasting adult patients are summarized in Table 1.

**Table 1: Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients**

Parameter	Mean $\pm$ SD (except where noted)
Oral bioavailability (%)	64 $\pm$ 10 (n = 5)
Apparent volume of distribution (L/kg)	1.6 $\pm$ 0.6 (n = 8)
Plasma protein binding (%)	<38
CSF:Plasma ratio <sup>a</sup>	0.6 [0.04 to 2.62] (n = 39)
Systemic clearance (L/hr/kg)	1.6 $\pm$ 0.6 (n = 6)
Renal clearance (L/hr/kg)	0.34 $\pm$ 0.05 (n = 9)
Elimination half-life (hr) <sup>b</sup>	0.5 to 3 (n = 19)

<sup>a</sup>Median [range]

<sup>b</sup>Approximate range

#### ***Distribution***

The apparent volume of distribution of zidovudine, following oral administration, is 1.6  $\pm$  0.6 L/kg; and binding to plasma protein is low, <38% (Table 1).

#### ***Metabolism and Elimination***

Zidovudine is primarily eliminated by hepatic metabolism. The major metabolite of zidovudine is GZDV. GZDV AUC is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74%, respectively, of the dose following oral administration. A second metabolite, 3'-amino-3' deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (I.V.) administration of zidovudine. The AMT AUC was one-fifth of the zidovudine AUC. Pharmacokinetics of zidovudine were dose-independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

#### ***Effect of Food on Absorption***

Zidovudine may be administered with or without food. The zidovudine AUC was similar when a single dose of zidovudine was administered with food.

### ***Special Populations***

#### ***Renal Impairment***

Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n = 14) following a single 200-mg oral dose (Table 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl)  $\geq 15$  mL/min.

**Table 2: Zidovudine Pharmacokinetic Parameters in Patients with Severe Renal Impairment<sup>a</sup>**

<b>Parameter</b>	<b>Control Subjects (Normal Renal Function) (n = 6)</b>	<b>Patients with Renal Impairment (n = 14)</b>
CrCl (mL/min)	120 $\pm$ 8	18 $\pm$ 2
Zidovudine AUC (ng•hr/mL)	1400 $\pm$ 200	3100 $\pm$ 300
Zidovudine half-life (hr)	1.0 $\pm$ 0.2	1.4 $\pm$ 0.1

<sup>a</sup>Data are expressed as mean  $\pm$  standard deviation.

#### ***Hemodialysis and Peritoneal Dialysis***

The pharmacokinetics and tolerance of zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks. Daily doses of 500mg or less were well tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis (see **DOSAGE AND ADMINISTRATION**).

#### ***Hepatic Impairment***

Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

#### ***Pediatric Patients***

Zidovudine pharmacokinetics has been evaluated in HIV-1 infected pediatric patients (Table 3).

*Patients 3 Months to 12 Years of Age*

Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m<sup>2</sup> every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After I.V. dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV (see **DOSAGE AND ADMINISTRATION**).

#### *Patients <3 Months of Age*

Zidovudine pharmacokinetics has been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine *in utero*. The half-life was 13.0 ± 5.8 hours. In neonates ≤14 days old, bioavailability was greater, total body clearance was slower, and the half-life was longer than in pediatric patients >14 days old. For dose recommendations for neonates, (see **DOSAGE AND ADMINISTRATION**).

**Table 3: Zidovudine Pharmacokinetic Parameters in Pediatric Patients<sup>a</sup>**

<b>Parameter</b>	<b>Birth to 14 Days of Age</b>	<b>14 Days to 3 Months of Age</b>	<b>3 Months to 12 Years of Age</b>
Oral bioavailability (%)	89 ± 19 (n = 15)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF: Plasma ratio	no data	no data	0.68 (0.03 to 3.25) <sup>b</sup> (n = 38)
CL (L/hr/kg)	0.65 ± 0.29 (n = 18)	1.14 ± 0.24 (n = 16)	1.85 ± 0.47 (n = 20)
Elimination half-life (hr)	3.1 ± 1.2 (n = 21)	1.9 ± 0.7 (n = 18)	1.5 ± 0.7 (n = 21)

<sup>a</sup> Data presented as mean ± standard deviation except where noted

<sup>b</sup> Median [range]

#### *Geriatric Patients*

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

#### *Gender*

A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no differences in zidovudine AUC when a single dose of zidovudine was administered as the 300-mg Zidovudine Tablet.

## **INDICATIONS**

**ZIDOVIR Capsules, Tablets and Oral Solution**, are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

### Prevention of Maternal-Fetal HIV-1 Transmission

Zidovudine is indicated for the prevention of maternal-fetal HIV-1 transmission (see **DOSAGE AND ADMINISTRATION**). The indication is based on a dosing regimen that included components:

1. antepartum therapy of HIV-1 infected mothers
2. intrapartum therapy of HIV-1 infected mothers
3. post-partum therapy of HIV-1 exposed neonate.

Points to consider prior to initiating zidovudine in pregnant women for the prevention of maternal-fetal HIV-1 transmission include:

- In most cases, zidovudine for prevention of maternal-fetal HIV-1 transmission should be given in combination with other antiretroviral drugs.
- Prevention of HIV-1 transmission in women who have received zidovudine for a prolonged period before pregnancy has not been evaluated.
- Because the fetus is most susceptible to the potential teratogenic effects of drugs during the first 10 weeks of gestation and the risks of therapy with zidovudine during that period are not fully known, women in the first trimester of pregnancy who do not require immediate initiation of antiretroviral therapy for their own health may consider delaying use; this indication is based on use after 14 weeks gestation.

### DOSAGE AND ADMINISTRATION

#### Adults

The recommended oral dose of **ZIDOVIR** is 600 mg/day in divided doses in combination with other antiretrovirals.

#### Pediatric Patients (4 weeks to <18 years of age)

Healthcare professionals should pay special attention to accurate calculation of the dose of zidovudine, transcription of the medication order, dispensing information, and dosing instructions to minimize risk for medication dosing errors.

Prescribers should calculate the appropriate dose of zidovudine for each child based on body weight (kg) and should not exceed the recommended adult dose. Before prescribing zidovudine capsules or tablets, children should be assessed for the ability to swallow capsules or tablets. If a child is unable to reliably swallow a zidovudine capsule or tablet, the zidovudine syrup formulation should be prescribed.

The recommended dosage in pediatric patients, 4 weeks of age and older and weighing  $\geq 4$  kg, is provided in Table 4. Zidovudine syrup should be used to provide accurate dosage when whole tablets or capsules are not appropriate.

**Table 4: Recommended Pediatric Dosage of Zidovudine**

Body Weight (kg)	Total Daily Dose	Dosage Regimen and Dose	
		b.i.d.	t.i.d.
4 to <9	24	12 mg/kg	8 mg/kg

	mg/kg/day		
≥9 to <30	18 mg/kg/day	9 mg/kg	6 mg/kg
≥30	600 mg/day	300 mg	200 mg

Alternatively, dosing for zidovudine can be based on body surface area (BSA) for each child. The recommended oral dose of zidovudine is 480 mg/m<sup>2</sup>/day in divided doses (240 mg/m<sup>2</sup> twice daily or 160 mg/m<sup>2</sup> three times daily). In some cases the dose calculated by mg/kg will not be the same as that calculated by the BSA.

### **Prevention of Maternal-Fetal HIV-1 Transmission**

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 labor. During labor and delivery, intravenous zidovudine should be administered at 2 mg/kg (total body weight) over 1 hour, followed by a continuous I.V. infusion of 1 mg/kg/hour (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.

### **Patients with Severe Anemia and/or Neutropenia**

Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (granulocyte count <750 cells/mm<sup>3</sup> or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see **WARNINGS AND PRECAUTIONS**). In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematological indices such as serum erythropoetin level and patient tolerance.

### **Patients with Renal Impairment**

#### ***End-Stage Renal Disease***

In patients maintained on hemodialysis or peritoneal dialysis, the recommended dosage is 100 mg every 6 to 8 hours.

### **Patients with Hepatic Impairment**

There are insufficient data to recommend dose adjustment of zidovudine in patients with mild to moderate impaired hepatic function or liver cirrhosis.

## CONTRAINDICATIONS

**ZIDOVIR Capsules, Tablets and Oral Solution** are contraindicated for patients who have had potentially life-threatening allergic reactions (eg, anaphylaxis, Stevens-Johnson syndrome) to any of the components of the formulations.

## WARNINGS AND PRECAUTIONS

### Drug Interactions

#### ***Antiretroviral Agents***

##### *Stavudine*

Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated *in vitro*.

##### *Nucleoside Analogues Affecting DNA Replication*

Some nucleoside analogues affecting DNA replication, such as ribavirin, antagonize the *in vitro* antiviral activity of zidovudine against HIV-1; concomitant use of such drugs should be avoided.

##### ***Doxorubicin***

Concomitant use of zidovudine with doxorubicin should be avoided since an antagonistic relationship has been demonstrated *in vitro*.

#### ***Hematological/Bone Marrow Suppressive/Cytotoxic Agents***

Co-administration of ganciclovir, interferon alfa, ribavirin, and other bone marrow suppressive or cytotoxic agents may increase the hematological toxicity of zidovudine.

**Table 5: Effect of Coadministered Drugs on Zidovudine AUC<sup>a</sup>**

Co-administered drug and dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of co-administered drug
			AUC	Variability	
Atovaquone 750 mg q12 hr with food	200 mg q 8 hr	14	↑AUC 31 %	Range 23% to 78% <sup>b</sup>	↔
Clarithromycin 500 mg twice daily	100mg q4hr x 7 days	4	↓AUC 12%	Range ↓34% to ↑14%	Not reported
Fluconazole 400 mg daily	200 mg q 8 hr	12	↑AUC 74 %	95% CI: 54 % to 98%	Not reported
Lamivudine 300 mg q 12 hr	Single 200 mg	12	↑AUC 13 %	90% CI: 2% to 27%	↔

Methadone 30 to 90 mg daily	200 mg q 4 hr	9	↑AUC 43 %	Range 16 % to 64 %	↔
Nelfinavir 750 mg q 8 hr x 7 to 10 days	Single 200 mg	11	↓AUC 35 %	Range 28 % to 41 %	↔
Probenecid 500 mg q 6 hr x 2 days	2 mg/kg q 8 hr x 3 days	3	↑AUC 106 %	Range 100 % to 170 % <sup>b</sup>	Not assessed
Rifampin 600 mg daily x 14 days	200 mg q 8 hr x 14 days	8	↓AUC 47 %	90% CI: 41% to 53 %	Not assessed
Ritonavir 300 mg q 6 hr x 4 days	200 mg q 8 hr x 4 days	9	↓AUC 25 %	95% CI: 15 % to 34%	↔
Valproic acid 250 mg or 500 mg q 8 hr x 4 days	100 mg q 8 hr x 4 days	6	↑AUC 80 %	Range 64 % to 130 % <sup>b</sup>	Not assessed

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.

<sup>a</sup>This table is not all inclusive.

<sup>b</sup>Estimated range of percent difference.

### ***Phenytoin***

Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-1-positive volunteers received a single 300 mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.

### ***Ribavirin***

*In vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected patients (see **WARNINGS AND PRECAUTIONS**)

### **Hematologic Toxicity/Bone Marrow Suppression**

**ZIDOVIR** should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count  $<1000$  cells/mm<sup>3</sup> or hemoglobin  $<9.5$  g/dL. Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with advanced symptomatic HIV-1 disease, anemia and neutropenia were the most significant adverse effects observed. In patients who experience hematologic toxicity, a reduction in hemoglobin may occur as early as 2 to 4 weeks, and neutropenia usually occurs after 6 to 8 weeks. There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuance of the drug. However, significant anemia (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.

Frequent blood counts are strongly recommended to detect severe anemia or neutropenia in patients with poor bone marrow reserve, particularly in patients with advanced HIV-1 disease who are treated with zidovudine. For HIV-1-infected individuals and patients with asymptomatic or early HIV-1 disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage interruption may be needed (see **DOSAGE AND ADMINISTRATION**).

### **Myopathy**

Myopathy and myositis with pathological changes, similar to that produced by HIV-1 disease, have been associated with the prolonged use of zidovudine.

### **Lactic Acidosis/Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged exposure to antiretroviral nucleoside analogues may be risk factors. Particular caution should be exercised when administering **ZIDOVIR** to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with **ZIDOVIR** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

### **Use with Interferon- and Ribavirin-Based Regimens in HIV-1/HCV Co-Infected Patients**

*In vitro* studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as zidovudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (eg, loss of HIV-1/HCV virologic suppression) was seen when ribavirin was co-administered with zidovudine in HIV-1/HCV co-infected patients, exacerbation of anemia due to ribavirin has been reported when zidovudine is part of the HIV-1 regimen. Co-administration of ribavirin and zidovudine is not advised. Consideration should be given to replacing zidovudine in established combination HIV-1/HCV therapy, especially in patients with a known history of zidovudine-induced anemia.

Hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and zidovudine should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia.

Discontinuation of zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (eg, Childs Pugh >6).

#### **Use with Other Zidovudine-Containing Products**

Zidovudine should not be administered with combination products that contain zidovudine as one of their components.

#### **Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including zidovudine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

#### **Fat Redistribution**

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance”, have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

#### **Renal Impairment**

In patients with severely impaired renal function (CrCl <15 mL/min), dosage reduction is recommended (see **DOSAGE AND ADMINISTRATION**).

## Hepatic Impairment

Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function, which may increase the risk of hematological toxicity (see **DOSAGE AND ADMINISTRATION**).

## Pregnancy

### *Pregnancy Category C*

In humans, treatment with zidovudine during pregnancy reduced the rate of maternal-fetal HIV-1 transmission from 24.9% for infants born to placebo-treated mothers to 7.8% for infants born to mothers treated with zidovudine. There were no differences in pregnancy-related adverse events between the treatment groups. Animal reproduction studies in rats and rabbits showed evidence of embryotoxicity and increased fetal malformations.

A randomized, double-blind, placebo-controlled trial was conducted in HIV-1-infected pregnant women to determine the utility of zidovudine for the prevention of maternal-fetal HIV-1-transmission. Congenital abnormalities occurred with similar frequency between neonates born to mothers who received zidovudine and neonates born to mothers who received placebo. The observed abnormalities included problems in embryogenesis (prior to 14 weeks) or were recognized on ultrasound before or immediately after initiation of the study drug.

Increased fetal resorptions occurred in pregnant rats and rabbits treated with doses of zidovudine that produced drug plasma concentrations, 66 to 226 times (rats) and 12 to 87 times (rabbits) the mean steady-state peak human plasma concentration following a single 100 mg dose of zidovudine. There were no other reported developmental anomalies. In another developmental toxicity study, pregnant rats received zidovudine up to near-lethal doses that produced peak plasma concentrations 350 times peak human plasma concentrations (300 times the daily exposure (AUC) in humans given 600 mg/day zidovudine). This dose was associated with marked maternal toxicity and an increased incidence of fetal malformations. However, there were no signs of teratogenicity at doses up to one-fifth the lethal dose.

## Lactation

Zidovudine is excreted in human milk. The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not to breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving **ZIDOVIR**.

### **Pediatric Use**

Zidovudine has been studied in HIV-1-infected pediatric patients  $\geq 6$  weeks of age who had HIV-1-related symptoms or who were asymptomatic with abnormal laboratory values indicating significant HIV-1-related immunosuppression. Zidovudine has also been studied in neonates perinatally exposed to HIV-1 (see **DOSAGE AND ADMINISTRATION, UNDESIRABLE EFFECTS**)

### **Geriatric Use**

Clinical studies of Zidovudine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## **UNDESIRABLE EFFECTS**

### **Clinical Trials Experience**

The following are the adverse reactions of Zidovudine:

- Hematological toxicity, including neutropenia and anemia (see **BOXED WARNINGS** and **WARNINGS AND PRECAUTIONS**).
- Symptomatic myopathy (see **BOXED WARNINGS** and **WARNINGS AND PRECAUTIONS**).
- Lactic acidosis and severe hepatomegaly with steatosis (see **BOXED WARNINGS** and **WARNINGS AND PRECAUTIONS**).
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C (see **WARNINGS AND PRECAUTIONS**).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### **Adults**

The frequency and severity of adverse reactions associated with the use of zidovudine are greater in patients with more advanced infection at the time of initiation of therapy. Table 6 summarizes events reported at a statistically significant greater incidence for patients receiving zidovudine in a monotherapy study:

**Table 6: Percentage (%) of Patients with Adverse Reactions<sup>a</sup> in Asymptomatic HIV-1 Infection (ACTG 019)**

	<b>Zidovudine 500 mg/day</b>	<b>Placebo</b>
<b>Adverse Reaction</b>	<b>(n = 453)</b>	<b>(n = 428)</b>

<b>Body as a Whole</b>		
Asthenia	9% <sup>b</sup>	6%
Headache	63%	53%
Malaise	53%	45%
<b>Gastrointestinal</b>		
Anorexia	20%	11%
Constipation	6% <sup>b</sup>	4%
Nausea	51%	30%
Vomiting	17%	10%

<sup>a</sup> Reported in ≥5% of the study population

<sup>b</sup> Not statistically significant versus placebo

In addition to the adverse events listed above, other adverse reactions observed at an incidence of >5% in any treatment arm in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, insomnia, musculoskeletal pain, myalgia, and neuropathy. Additionally, in these studies hyperbilirubinemia was reported at an incidence of ≤0.8%.

Selected laboratory abnormalities observed during a clinical study of monotherapy with zidovudine are shown in Table 7.

**Table 7: Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients with Asymptomatic HIV-1 Infection (ACTG 019)**

Test (Abnormal Level)	Zidovudine 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb <8 g/dL)	1%	<1%
Granulocytopenia (<750 cells/mm <sup>3</sup> )	2%	2%
Thrombocytopenia (platelets <50,000/mm <sup>3</sup> )	0%	<1%
ALT (>5 x ULN)	3%	3%
AST (>5 x ULN)	1%	2%

ULN = Upper limit of normal

### ***Pediatrics***

The clinical adverse reactions reported among adult recipients of zidovudine may also occur in pediatric patients.

Selected clinical adverse reactions and physical findings with a >5% frequency during therapy with lamivudine oral suspension 4 mg/kg twice daily plus zidovudine 160 mg/m<sup>2</sup> three times daily compared with didanosine in therapy-naïve (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 8.

**Table 8: Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG 300**

<b>Adverse Reaction</b>	<b>Lamivudine plus Zidovudine (n = 236)</b>	<b>Didanosine (n = 235)</b>
<b>Body as a Whole</b>		
Fever	25%	32%
<b>Digestive</b>		
Hepatomegaly	11%	11%
Nausea and vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
<b>Respiratory</b>		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
<b>Ear, Nose, and Throat</b>		
Signs or symptoms of ears <sup>a</sup>	7%	6%
Nasal discharge or congestion	8%	11%
<b>Other</b>		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

<sup>a</sup>Includes pain, discharge, erythema, or swelling of an ear

Selected laboratory abnormalities experienced by therapy-naïve (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 9.

**Table 9: Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG300**

<b>Test (Abnormal Level)</b>	<b>Lamivudine plus Zidovudine</b>	<b>Didanosine</b>
Neutropenia (ANC <400 cells/mm <sup>3</sup> )	8%	3%
Anemia (Hgb <7.0 g/dL)	4%	2%
Thrombocytopenia (platelets <50,000/mm <sup>3</sup> )	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal

ANC = Absolute neutrophil count

Macrocytosis was reported in the majority of pediatric patients receiving zidovudine 180 mg/m<sup>2</sup> every 6 hours in open-label studies. Additionally, adverse

reactions reported at an incidence of <6% in these studies were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, nervousness/irritability, and weight loss.

### ***Use for the Prevention of Maternal-Fetal Transmission of HIV-1***

In a randomized, double-blind, placebo-controlled trial in HIV-1-infected women and their neonates conducted to determine the utility of zidovudine for the prevention of maternal-fetal HIV-1 transmission, zidovudine syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates, beginning within 12 hours following birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0g/dL) and neutropenia (<1000 cells/mm<sup>3</sup>). Anemia occurred in 22% of the neonates who received zidovudine and in 12% of the neonates who received placebo.

The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving zidovudine, compared to neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with zidovudine. Neutropenia was reported with similar frequency in the group that received zidovudine (21%) and in the group that received placebo (27%). The long-term consequences of *in utero* and infant exposure to zidovudine are unknown.

### **Observed During Clinical Practice**

In addition to adverse events reported from clinical trials, the following events have been identified during use of zidovudine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to their seriousness, frequency of reporting, potential causal connection to zidovudine, or a combination of these factors.

***Body as a Whole:*** Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat (see **WARNINGS AND PRECAUTIONS**)

***Cardiovascular:*** Cardiomyopathy, syncope.

***Endocrine:*** Gynecomastia.

***Eye:*** Macular edema.

***Gastrointestinal:*** Dysphagia, flatulence, oral mucosa pigmentation, mouth ulcers.

***General:*** Sensitization reactions, including anaphylaxis and angioedema, vasculitis.

***Hemic and Lymphatic:*** Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.

**Hepatobiliary Tract and Pancreas:** Hepatitis, hepatomegaly with steatosis, jaundice, lactic acidosis, pancreatitis.

**Musculoskeletal:** Increased CPK, increased LDH, muscle spasm, myopathy and myositis with pathological changes (similar to that produced by HIV-1 disease), rhabdomyolysis, tremor.

**Nervous:** Anxiety, confusion, depression, dizziness, loss of mental acuity, mania, paresthesia, seizures, somnolence, vertigo.

**Respiratory:** Dyspnea, rhinitis, sinusitis.

**Skin:** Changes in skin and nail pigmentation, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, sweat, urticaria.

**Special Senses:** Amblyopia, hearing loss, photophobia, taste perversion.

**Urogenital:** Urinary frequency, urinary hesitancy.

## **OVERDOSAGE**

Acute overdoses of zidovudine have been reported in pediatric patients and adults. These involved exposures up to 50 grams. No specific symptoms or signs have been identified following acute overdosage with zidovudine apart from those listed as adverse events such as fatigue, headache, vomiting, and occasional reports of hematological disturbances. All patients recovered without permanent sequelae. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, 3' azido-3'-deoxy-5'-O- $\beta$ -D-glucopyranuronosylthymidine GZDV, is enhanced.

## **PACKAGING INFORMATION**

**ZIDOVIR-100 Capsules**.....Strip pack of 10 capsules

**ZIDOVIR-300 Tablets**.....Strip pack of 10 tablets

**ZIDOVIR Oral Solution**..... Bottle of 100 ml with syringe

*Last updated: October 2010*