HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use zidovudine safely and effectively. See full prescribing information for zidovudine.

Zidovudine Tablets, USP

Initial U.S. Approval: 1987

WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS.

See full prescribing information for complete boxed warning.

- **Hematologic toxicity including neutropenia and severe anemia have been associated with the use of zidovudine. (5.1)**
- **Symptomatic myopathy associated with prolonged use of zidovudine. (5.2)**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including zidovudine. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.3)**

----------INDICATIONS AND USAGE----------

Zidovudine is a nucleoside analogue reverse transcriptase inhibitor indicated for:

- Treatment of Human Immunodeficiency Virus (HIV-1) infection in combination with other antiretroviral agents. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Treatment of HIV-1 infection:
  Pediatric patients (4 weeks to <18 years of age and who weigh 4 kg and greater): Dosage should be calculated based on body weight not to exceed adult dose. (2.1)
- Patients with severe anemia and/or neutropenia:
  Dosage interruption may be necessary. (2.2)
- Renal Impairment – The appropriate dose adjustment for pediatric patients on hemodialysis or peritoneal dialysis is not known. (2.3)

----------DOSAGE FORMS AND STRENGTHS-- ----------

Tablets: Scored 60 mg (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to zidovudine (e.g., anaphylaxis, Stevens-Johnson syndrome). (4)

----------WARNINGS AND PRECAUTIONS----------

- Hematologic toxicity/bone marrow suppression including neutropenia and severe anemia have been associated with the use of zidovudine. (5.1)
- Symptomatic myopathy associated with prolonged use of zidovudine. (5.2)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including zidovudine. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.3)
- Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised. (5.4)
- Hepatic decompensation, (some fatal), has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue zidovudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Zidovudine should not be administered with other zidovudine-containing combination products. (5.5)
- Immune reconstitution syndrome (5.6) and redistribution/accumulation of body fat (5.7) have been reported in patients treated with combination antiretroviral therapy.

----------ADVERSE REACTIONS----------

- Most commonly reported adverse reactions (incidence ≥15%) in adult HIV-1 clinical studies were headache, malaise, nausea, anorexia, and vomiting. (6.1)
- Most commonly reported adverse reactions (incidence ≥15%) in pediatric HIV-1 clinical studies were fever, cough, and digestive disorders. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Stavudine: Concomitant use with zidovudine should be avoided. (7.1)
- Doxorubicin: Use with zidovudine should be avoided. (7.2)
- Bone marrow suppressive/cytotoxic agents: May increase the hematologic toxicity of zidovudine. (7.3)

See 17 for PATIENT COUNSELING INFORMATION.

Issued: December 2010

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF HEMATOLOGICAL TOXICITY, MYOPATHY, LACTIC ACIDOSIS

Zidovudine tablets has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV-1 disease *[see Warnings and Precautions (5.1)]*.

Prolonged use of zidovudine has been associated with symptomatic myopathy *[see Warnings and Precautions (5.2)]*.

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 (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1

Zidovudine, a nucleoside reverse transcriptase inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of HIV-1 Infection

Pediatric Patients (4 weeks to <18 years of age who weigh 4 kg or greater): 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 tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a zidovudine tablet, the method of preparation procedure listed below should be followed or the zidovudine syrup formulation should be prescribed.

The recommended dosage in pediatric patients 4 weeks of age and older and weighing greater than or equal to 4 kg is provided in Table 1. Zidovudine syrup should be used to provide accurate dosage in pediatric patients who weigh less than 4 kg.

Table 1. Recommended Pediatric Dosage of Zidovudine Tablets

Body Weight (kg)	Dosage Regimen Using Scored 60 mg Tablets		Total Daily Dose
	AM Dose	PM Dose	
4 to 6	1 tablet (60 mg)	1 tablet (60 mg)	120 mg
6.1 to 11	1.5 tablet (90 mg)	1.5 tablet (90 mg)	180 mg
11.1 to 14	2 tablets (120 mg)	2 tablets (120 mg)	240 mg
14.1 to 18	2.5 tablets (150 mg)	2.5 tablets (150 mg)	300 mg
18.1 to 22	3 tablets (180 mg)	3 tablets (180 mg)	360 mg
22.1 to 25	3.5 tablets (210 mg)	3.5 tablets (210 mg)	420 mg
25.1 to 28	4 tablets (240 mg)	4 tablets (240 mg)	480 mg
28.1 to < 30	4.5 tablets (270 mg)	4.5 tablets (270 mg)	540 mg
≥30	5 tablets (300 mg)*	5 tablets (300 mg)*	600 mg

* For recommended doses of 300 mg twice daily, the adult formulation (300 mg tablet) can be use.

Safety and efficacy have not been established in patients weighing less than 4 kg.

Method of Preparation

For children unable to swallow the tablet(s), the following procedure can be used:

1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet(s) breaks up into pieces small enough for the child to swallow; a spoon can be used to crush the pieces, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX ZIDOVUDINE TABLET(S) WITH ANY LIQUID OTHER THAN WATER.

2.2 Patients With Severe Anemia and/or Neutropenia

Significant anemia (hemoglobin <7.5 g/dL or reduction >25% of baseline) and/or significant neutropenia (granulocyte count <750 cells/mm^3 or reduction >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed *[see Warnings and Precautions (5.1)]*. 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 hematologic indices such as serum erythropoetin level and patient tolerance.

2.3 Patients With Renal Impairment

End-Stage Renal Disease: In adult patients maintained on hemodialysis or peritoneal dialysis, the recommended dosage is 100 mg every 6 to 8 hours. The appropriate dose adjustment for pediatric patients maintained on hemodialysis or peritoneal dialysis is not known *[see Clinical Pharmacology (12.3)]*.

2.4 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.

3 DOSAGE FORMS AND STRENGTHS

Zidovudine Tablets USP, 60 mg are scored, white colored, biconvex, capsule shaped bevel edged film-coated tablets, debossed with "4" and "1" on either side of deep breakline on one side and "H" on other side.

4 CONTRAINDICATIONS

Zidovudine tablets are contraindicated in patients who have had potentially life-threatening allergic reactions (e.g., anaphylaxis, Stevens-Johnson syndrome) to any of the components of this formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Toxicity/Bone Marrow Suppression

Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 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 events 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 (2.2)]*.

5.2 Myopathy

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

5.3 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 zidovudine 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 zidovudine 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).

5.4 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 (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with zidovudine in HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, exacerbation of anemia due to ribavirin has been reported when zidovudine is part of the HIV regimen. Coadministration 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 (e.g., Child Pugh >6) (see the complete prescribing information for interferon and ribavirin).

5.5 Use With Other Zidovudine-Containing Products

Zidovudine should not be administered with combination products that contain zidovudine as one of their components [e.g., RETROVIR® (zidovudine), COMBIVIR® (lamivudine and zidovudine) or TRIZIVIR® (abacavir, lamivudine and zidovudine)].

5.6 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 systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

5.7 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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hematologic toxicity, including neutropenia and anemia *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Symptomatic myopathy *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C *[see Warnings and Precautions (5.4)]*.

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 2 summarizes events reported at a statistically significant greater incidence for patients receiving zidovudine in a monotherapy study.

Table 2. Percentage (%) of Patients With Adverse Reactions[a] in Asymptomatic HIV-1 Infection (ACTG 019)

Adverse Reaction	Zidovudine 500 mg/day (n = 453)	Placebo (n = 428)
Body as a whole		
Asthenia	9%[b]	6%
Headache	63%	53%
Malaise	53%	45%
Gastrointestinal		
Anorexia	20%	11%
Constipation	6%[b]	4%
Nausea	51%	30%
Vomiting	17%	10%

[a] Reported in ≥5% of study population.
[b] Not statistically significant versus placebo.

In addition to the adverse reactions listed in Table 2, adverse reactions observed at an incidence of ≥5% in any treatment arm in clinical studies (NUCA3001, NUCA3002, NUCB3001, and NUCB3002) 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 3.

Table 3. 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^3)	2%	2%
Thrombocytopenia (platelets<50,000/mm^3)	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.

Study ACTG300: 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^2 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 4.

Table 4. Selected Clinical Adverse Reactions and Physical Findings (≥5% Frequency) in Pediatric Patients in Study ACTG300

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

[a] Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are listed in Table 5.

Table 5. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients in Study ACTG300

Test (Abnormal Level)	Lamivudine plus Zidovudine	Didanosine
Neutropenia (ANC<400 cells/mm^3)	8%	3%
Anemia (Hgb<7.0 g/dL)	4%	2%
Thrombocytopenia (platelets<50,000/mm^3)	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^2 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.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following reactions have been identified during postmarketing use of zidovudine. 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 a combination of their seriousness, frequency of reporting, or potential causal connection to zidovudine.

Body as a Whole: Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat *[see Warnings and Precautions (5.6)]*.

Cardiovascular: Cardiomyopathy, syncope.

Endocrine: Gynecomastia.

Eye: Macular edema.

Gastrointestinal: Dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

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.

7 DRUG INTERACTIONS

7.1 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.

7.2 Doxorubicin

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

7.3 Hematologic/Bone Marrow Suppressive/Cytotoxic Agents

Coadministration of ganciclovir, interferon alfa, ribavirin, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

8 USE IN SPECIFIC POPULATIONS

8.1 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 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 *[see Nonclinical Toxicology (13.2)]*.

Antiretroviral pregnancy registry: To monitor maternal-fetal outcomes of pregnant women exposed to zidovudine, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

Zidovudine is excreted in human milk *[see Clinical Pharmacology (12.3)]*.

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not 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 zidovudine.

8.4 Pediatric Use

Zidovudine has been studied in HIV-1-infected pediatric patients ≥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 (2.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

8.5 Geriatric Use

Clinical studies of zidovudine did not include sufficient numbers of subjects aged 65 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.

8.6 Renal Impairment

In patients with severely impaired renal function (CrCl<15 mL/min), dosage reduction is recommended *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

8.7 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

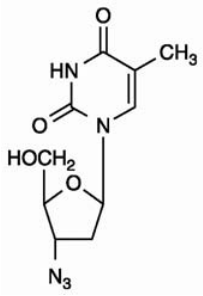
to be increased in patients with severely impaired hepatic function which may increase the risk of hematologic toxicity *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

10 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*-β-*D*-glucopyranuronosylthymidine (GZDV), is enhanced.

11 DESCRIPTION

Zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against HIV-1. The chemical name of zidovudine is 3'-azido-3'-deoxythymidine; it has the following structural formula:



Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

Zidovudine tablets are for oral administration. Each film-coated tablet contains 60 mg of zidovudine and the inactive ingredients microcrystalline cellulose, hypromellose, sodium starch glycolate, magnesium stearate, titanium dioxide, and PEG 400.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zidovudine is an antiviral agent *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

Adults: The rate and extent of absorption of zidovudine from the 300 mg tablets were bioequivalent to that from RETROVIR® tablets containing zidovudine 300 mg when administered to healthy volunteers in the fasted and fed state.

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 6.

Table 6. Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients

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

[a] Median [range].

[b] Approximate range.

Distribution: The apparent volume of distribution of zidovudine, following oral administration, is 1.6 ± 0.6 L/kg; and binding to plasma protein is low, <38% (Table 6).

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 (IV) 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 under both fasted and fed conditions.

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 7). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl) ≥15 mL/min.

Table 7. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment[a]

Parameter	Control Subjects (Normal Renal Function) (n = 6)	Patients With Renal Impairment (n = 14)
CrCl (mL/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng•hr/mL)	1,400 ± 200	3,100 ± 300
Zidovudine half-life (hr)	1.0 ± 0.2	1.4 ± 0.1

[a] Data are expressed as mean ± 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 500 mg 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 (2.3)]*.

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 (2.4)]*.

Pediatric Patients: Zidovudine pharmacokinetics have been evaluated in HIV-1-infected pediatric patients (Table 8).

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^2 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 intravenous 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 (2.1)]*.

Patients <3 Months of Age: Zidovudine pharmacokinetics have 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 half-life was longer than in pediatric patients >14 days old.

Table 8. Zidovudine Pharmacokinetic Parameters in Pediatric Patients[a]

Parameter	14 Days to 3 Months of Age	3 Months to 12 Years of Age
Oral bioavailability (%)	61 ± 19 (n = 17)	65 ± 24 (n = 18)
CSF: plasma ratio	no data	0.68 [0.03 to 3.25][b] (n = 38)
CL (L/hr/kg)	1.14 ± 0.24 (n = 16)	1.85 ± 0.47 (n = 20)
Elimination half-life (hr)	1.9 ± 0.7 (n = 18)	1.5 ± 0.7 (n = 21)

[a] Data presented as mean ± standard deviation except where noted.
[b] Median [range].

Pregnancy: Zidovudine pharmacokinetics have been studied in a Phase I study of 8 women during the last trimester of pregnancy. Zidovudine pharmacokinetics were similar to those of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery *[see Use in Specific Populations (8.1)]*.

Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. After administration of a single dose of 200 mg zidovudine to 13 HIV-1-infected women, the mean concentration of zidovudine was similar in human milk and serum *[see Use In Specific Populations (8.3)]*.

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.

Drug Interactions: *[See Drug Interactions (7)]*.

Table 9. Effect of Coadministered Drugs on Zidovudine AUC[a]

Note: ROUTINE DOSE MODIFICATION OF ZIDOVUDINE IS NOT WARRANTED WITH COADMINISTRATION OF THE FOLLOWING DRUGS.					
Coadministered Drug and Dose	Zidovudine Dose	n	Zidovudine Concentrations		Concentration of Coadministered Drug
			AUC	Variability	
Atovaquone 750 mg q 12 hr with food	200 mg q 8 hr	14	↑AUC 31%	Range 23% to 78%[b]	↔
Clarithromycin 500 mg twice daily	100 mg q 4 hr 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%[b]	↔
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%[b]	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%[b]	Not Assessed

↑ = Increase; ↓ = Decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = confidence interval.
[a] This table is not all inclusive.
[b] 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 (5.4)]*.

12.4 Microbiology

Mechanism of Action: 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 α and γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity: The antiviral activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The EC_{50} and EC_{90} values for zidovudine were 0.01 to 0.49 µM (1 µM = 0.27 mcg/mL) and 0.1 to 9 µM, respectively. HIV-1 from therapy-naive subjects with no mutations associated with resistance gave median EC_{50} values of 0.011 µM (range: 0.005 to 0.11 µM) from Virco (n = 92 baseline samples from COL40263) and 0.0017 µM (0.006 to 0.034 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of zidovudine against different HIV-1 clades (A-G) ranged from 0.00018 to 0.02 µM, and against HIV-2 isolates from 0.00049 to 0.004 µM. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with the nucleoside reverse transcriptase inhibitors abacavir, didanosine, and lamivudine; the non-nucleoside reverse transcriptase inhibitors delavirdine and nevirapine; and the protease inhibitors indinavir, nelfinavir, ritonavir, and saquinavir; and additive activity with interferon alfa. Ribavirin has been found to inhibit the phosphorylation of zidovudine in cell culture.

Resistance: Genotypic analyses of the isolates selected in cell culture and recovered from zidovudine-treated patients showed mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance. In general, higher levels of resistance were associated with greater number of amino acid substitutions. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of substitutions conferring resistance to zidovudine.

Cross-Resistance: In a study of 167 HIV-1-infected patients, isolates (n = 2) with multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of resistance-associated amino acid substitutions with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the Q151M substitution being most commonly associated with multi-drug resistance. The substitution at codon 151 in combination with substitutions at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine. Thymidine analogue mutations (TAMs) are selected by zidovudine and confer cross-resistance to abacavir,

didanosine, stavudine, tenofovir, and zalcitabine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Zidovudine was administered orally at 3 dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60, and 120 mg/kg/day in mice and 80, 220, and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30, and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, 7 late-appearing (after 19 months) vaginal neoplasms (5 nonmetastasizing squamous cell carcinomas, 1 squamous cell papilloma, and 1 squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle-dose animal. No vaginal tumors were found at the lowest dose.

In rats, 2 late-appearing (after 20 months), nonmetastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle dose in rats. No other drug-related tumors were observed in either sex of either species.

At doses that produced tumors in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 3 times (mouse) and 24 times (rat) the estimated human exposure at the recommended therapeutic dose of 100 mg every 4 hours.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Zidovudine was mutagenic in a 5178Y/TK$^{+/-}$ mouse lymphoma assay, positive in an in vitro cell transformation assay, clastogenic in a cytogenetic assay using cultured human lymphocytes, and positive in mouse and rat micronucleus tests after repeated doses. It was negative in a cytogenetic study in rats given a single dose.

Zidovudine, administered to male and female rats at doses up to 7 times the usual adult dose based on body surface area, had no effect on fertility judged by conception rates.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine administered in this study produced zidovudine exposures approximately 3 times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumors was noted with no increase in tumors in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body

weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumors in the lung, liver, and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine.

13.2 Reproductive and Developmental Toxicology Studies

Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated AUC in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

14 CLINICAL STUDIES

Therapy with zidovudine has been shown to prolong survival and decrease the incidence of opportunistic infections in patients with advanced HIV-1 disease and to delay disease progression in asymptomatic HIV-1-infected patients.

14.1 Adults

Combination Therapy: Zidovudine in combination with other antiretroviral agents has been shown to be superior to monotherapy for one or more of the following endpoints: delaying death, delaying development of AIDS, increasing CD4+ cell counts, and decreasing plasma HIV-1 RNA.

The clinical efficacy of a combination regimen that includes zidovudine was demonstrated in study ACTG320. This study was a multi-center, randomized, double-blind, placebo-controlled trial that compared zidovudine 600 mg/day plus lamivudine 300 mg/day to zidovudine plus lamivudine plus indinavir 800 mg t.i.d. The incidence of AIDS-defining events or death was lower in the triple-drug–containing arm compared with the 2-drug–containing arm (6.1% versus 10.9%, respectively).

Monotherapy: In controlled studies of treatment-naive patients conducted between 1986 and 1989, monotherapy with zidovudine, as compared with placebo, reduced the risk of HIV-1 disease progression, as assessed using endpoints that included the occurrence of HIV-1-related illnesses, AIDS-defining events, or death. These studies enrolled patients with advanced disease (BW002), and asymptomatic or mildly symptomatic disease in patients with CD4+ cell counts between 200 and 500 cells/mm^3 (ACTG016 and ACTG019). A

survival benefit for monotherapy with zidovudine was not demonstrated in the latter 2 studies. Subsequent studies showed that the clinical benefit of monotherapy with zidovudine was time limited.

14.2 Pediatric Patients

ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of lamivudine plus zidovudine with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive (≤56 days of antiretroviral therapy) pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The mean baseline CD4+ cell count was 868 cells/mm^3 (mean: 1,060 cells/mm^3 and the range: 0 to 4,650 cells/mm^3 for patients ≤5 years of age; mean: 419 cells/mm^3 and range: 0 to 1,555 cells/mm^3 for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL. The median duration on study was 10.1 months for the patients receiving lamivudine plus zidovudine and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 10.

Table 10. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
HIV-1 disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

16 HOW SUPPLIED/STORAGE AND HANDLING

Zidovudine Tablets USP, 60 mg are scored, white colored, biconvex, capsule shaped bevel edged film-coated tablets, debossed with “4” and “1” on either side of deep breakline on one side and “H” on other side.

Bottles of 60	NDC 65862-348-60
Bottles of 1000	NDC 65862-348-99

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Information About Therapy With Zidovudine

Neutropenia and Anemia: Patients should be informed that the major toxicities of zidovudine are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the

course of their infection. Patients should be informed that if toxicity develops, they may require transfusions or drug discontinuation. Patients should be informed of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV-1 disease *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Myopathy: Patients should be informed that myopathy and myositis with pathological changes, similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Lactic Acidosis/Hepatomegaly: Patients should be informed that some HIV medicines, including zidovudine, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Boxed Warning, Warnings and Precautions (5.3)]*.

HIV-1/HCV Co-Infection: Patients with HIV-1/HCV co-infection should be informed that 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 *[see Warnings and Precautions (5.4)]*.

Redistribution/Accumulation of Body Fat: Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.6)]*.

Common Adverse Reactions: Patients should be informed that the most commonly reported adverse reactions in adult patients being treated with zidovudine were headache, malaise, nausea, anorexia, and vomiting. The most commonly reported adverse reactions in pediatric patients receiving zidovudine were fever, cough, and digestive disorders. Patients also should be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with zidovudine *[see Adverse Reactions (6)]*.

Drug Interactions: Patients should be cautioned about the use of other medications, including ganciclovir, interferon alfa, and ribavirin, which may exacerbate the toxicity of zidovudine *[see Drug Interactions (7)]*.

Pregnancy: Pregnant women considering the use of zidovudine during pregnancy for prevention of HIV-1 transmission to their infants should be informed that transmission may still occur in some cases despite therapy. The long-term consequences of in utero and infant exposure to zidovudine are unknown, including the possible risk of cancer *[see Use in Specific Populations (8.1)]*.

HIV-1-infected pregnant women should be informed not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected *[see Use in Specific Populations (8.1)]*.

Information About Therapy With Zidovudine: Zidovudine is not a cure for HIV-1 infection, and patients may continue to acquire illnesses associated with HIV-1 infection, including opportunistic infections. Therefore, patients should be informed to seek medical care for any significant change in their health status.

Patients should be informed of the importance of taking zidovudine exactly as prescribed. They should be informed not to share medication and not to exceed the recommended dose. Patients should be informed that the long-term effects of zidovudine are unknown at this time.

Patients should be informed that therapy with zidovudine has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.

17.2 Method of Preparation

For children unable to swallow the tablet(s), the following procedure can be used:

1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet(s) breaks up into pieces small enough for the child to swallow; a spoon can be used to crush the pieces, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX ZIDOVUDINE TABLET(S) WITH ANY LIQUID OTHER THAN WATER.

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