# ZIDOVUDINE - zidovudine syrup
## Aurobindo Pharma Limited

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**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 syrup (zidovudine oral solution, USP).**

**ZIDOVUDINE Syrup (Zidovudine Oral Solution, USP) for oral use**
**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. (5.3)**
- **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. (5.4)**

**INDICATIONS AND USAGE**

Zidovudine oral solution, USP 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)
- Prevention of maternal-fetal HIV-1 transmission. (1.2)

**DOSAGE AND ADMINISTRATION**

- Treatment of HIV-1 infection:
  Adults: Recommended oral dosage is 300 mg twice a day with other antiretroviral agents. (2.1)

Pediatric patients (aged 4 weeks to less than 18 years): Dosage should be calculated based on body weight not to exceed adult dose. (2.2)

- Prevention of maternal-fetal HIV-1 transmission:
  Specific dosage instructions for mother and infant. (2.3)
- Patients with severe anemia and/or neutropenia:
  Dosage interruption may be necessary. (2.4)
- Renal impairment: Recommended oral dosage in hemodialysis or peritoneal dialysis or in patients with creatinine clearance (CrCl) less than 15 mL per minute is 100 mg every 6 to 8 hours. (2.5)

**DOSAGE FORMS AND STRENGTHS**

- Syrup: 10 mg per mL (3)

**CONTRAINDICATIONS**

Hypersensitivity to zidovudine or any of the components (e.g., anaphylaxis, Stevens-Johnson syndrome). (4)

**WARNINGS AND PRECAUTIONS**

- See boxed warning for information about the following: Hematologic toxicity, myopathy, and lactic acidosis and severe hepatomegaly. (5.1, 5.3, 5.4)
- 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. (5.5)
- 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. (5.5)
- Zidovudine should not be administered with other zidovudine-containing combination products. (5.6)

- Immune reconstitution syndrome (5.7) and redistribution/ accumulation of body fat (5.8) have been reported in patients treated with combination antiretroviral therapy.

**ADVERSE REACTIONS**

- Most commonly reported adverse reactions (incidence greater than or equal to 15%) in adult HIV-1 clinical trials were headache, malaise, nausea, anorexia, and vomiting. (6.1)
- Most commonly reported adverse reactions (incidence greater than or equal to 15%) in pediatric HIV-1 clinical trials were fever and cough. (6.1)
- Most commonly reported adverse reactions in neonates (incidence greater than or equal to 15%) in the prevention of maternal-fetal transmission of HIV-1 clinical trial were anemia and neutropenia. (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.**

**Revised: 2/2015**

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## FULL PRESCRIBING INFORMATION

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

**Hematologic Toxicity**

**Zidovudine syrup 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)]*.**

**Myopathy**

**Prolonged use of zidovudine has been associated with symptomatic myopathy *[see Warnings and Precautions (5.3)]*.**

**Lactic Acidosis and Severe Hepatomegaly**

**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 (5.4)]*.**

## 1 INDICATIONS AND USAGE

### 1.1 Treatment of HIV-1

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

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

Zidovudine oral solution, USP is indicated for the prevention of maternal-fetal HIV-1 transmission *[see Dosage and Administration (2.3)]*. The indication is based on a dosing regimen that included 3 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 oral solution, USP in pregnant women for the prevention of maternal-fetal HIV-1 transmission include:

- In most cases, zidovudine oral solution, USP 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 oral solution, USP 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 oral solution, USP 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.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Adults-Treatment of HIV-1 Infection

Oral Dosing

The recommended oral dose of zidovudine oral solution is 300 mg twice daily in combination with other antiretroviral agents.

### 2.2 Pediatric Patients (Aged 4 Weeks to Less than 18 Years)

Healthcare professionals should pay special attention to accurate calculation of the dose of zidovudine oral solution, 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 oral solution 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 (zidovudine oral solution, USP) formulation should be prescribed.

The recommended oral dosage in pediatric patients 4 weeks to less than 18 years and weighing greater than or equal to 4 kg is provided in Table 1. Zidovudine oral solution should be used to provide accurate dosage when whole tablets or capsules are not appropriate.

**Table 1: Recommended Pediatric Oral Dosage of Zidovudine Oral Solution**

| Body Weight (kg) | Total Daily Dose | Dosage Regimen and Dose | |
|---|---|---|---|
| | | Twice Daily | Three Times Daily |
| 4 to <9 | 24 mg/kg/day | 12 mg/kg | 8 mg/kg |
| ≥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 oral solution can be based on body surface area (BSA) for each child. The recommended oral dose of zidovudine oral solution is 480 mg per $m^2$ per day in divided doses (240 mg per $m^2$ twice daily or 160 mg per $m^2$ three times daily). In some cases the dose calculated by mg per kg will not be the same as that calculated by BSA.

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

The recommended dosage regimen for administration to pregnant women (greater than 14 weeks of pregnancy) and their neonates is:

Maternal Dosing: 100 mg orally 5 times per day until the start of labor *[see Clinical Studies (14.3)]*. During labor and delivery, intravenous zidovudine should be administered at 2 mg per kg (total body weight) over 1 hour followed by a continuous intravenous infusion of 1 mg per kg per hour (total body weight) until clamping of the umbilical cord.

Neonatal Dosing: Start neonatal dosing within 12 hours after birth and continue through 6 weeks of age. Neonates unable to receive oral dosing may be administered zidovudine intravenously. See Table 2.

**Table 2. Recommended Neonatal Dosages of Zidovudine**

| Route | Total Daily Dose | Dose and Dosage Regimen |
|---|---|---|
| Oral | 8 mg/kg/day | 2 mg/kg every 6 hours |
| Intravenous | 6 mg/kg/day | 1.5 mg/kg infused over 30 minutes, every 6 hours |

### 2.4 Patients With Severe Anemia and/or Neutropenia

Significant anemia (hemoglobin less than 7.5 g per dL or reduction greater than 25% of baseline) and/or significant neutropenia (granulocyte count less than 750 cells per $mm^3$ or reduction greater than 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.

### 2.5 Patients With Renal Impairment

In patients maintained on hemodialysis or peritoneal dialysis or with creatinine clearance (CrCl) by Cockcroft-Gault less than 15 mL per min, the recommended oral dosage is 100 mg every 6 to 8 hours *[see Use in Specific Populations (8.6),Clinical Pharmacology (12.3)]*.

### 2.6 Patients With Hepatic Impairment

There are insufficient data to recommend dose adjustment of zidovudine oral solution in patients with impaired hepatic function or liver cirrhosis. Frequent monitoring of hematologic toxicities is advised *[see Use in Specific Populations (8.7)]*.

## 3 DOSAGE FORMS AND STRENGTHS

**Zidovudine Syrup (Zidovudine Oral Solution, USP), 10 mg/mL** is (colorless to pale yellow, strawberry-flavored) containing 10 mg zidovudine in each (mL).

## 4 CONTRAINDICATIONS

Zidovudine oral solution is contraindicated in patients who have had potentially life-threatening hypersensitivity reaction (e.g., anaphylaxis, Stevens-Johnson syndrome) to any of the components of the 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 less than 1,000 cells per $mm^3$ or hemoglobin less than 9.5 g per 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 (2.4)]*.

### 5.3 Myopathy

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

### 5.4 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).

### 5.5 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 subjects *[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 greater than 6) (see the complete prescribing information for interferon and ribavirin).

### 5.6 Use with Other Zidovudine-containing Products

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

### 5.7 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 jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

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

### 5.8 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

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 (5.3)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.4)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C *[see Warnings and Precautions (5.5)]*.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with 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 3 summarizes adverse reactions reported at a statistically significant greater incidence for subjects receiving oral zidovudine in a monotherapy trial.

**Table 3. Percentage (%) of Subjects with Adverse Reactions (Greater than or Equal to 5% Frequency) in Asymptomatic HIV-1 Infection (ACTG 019)**

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

[a]Not statistically significant versus placebo.

In addition to the adverse reactions listed in Table 3, adverse reactions observed at an incidence of greater than or equal to 5% in any treatment arm in clinical trials (NUCA3001, NUCA3002, NUCB3001, and NUCB3002) were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue, insomnia, musculoskeletal pain, myalgia, and neuropathy. Additionally, in these trials hyperbilirubinemia was reported at an incidence of less than or equal to 0.8%.

Selected laboratory abnormalities observed during a clinical trial of monotherapy with oral zidovudine are shown in Table 4.

**Table 4. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Subjects 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.

*Trial ACTG 300:* Selected clinical adverse reactions and physical findings with a greater than or equal to 5% frequency during therapy with EPIVIR® (lamivudine) oral suspension 4 mg per kg twice daily plus zidovudine 160 mg per $m^2$ 3 times daily compared with didanosine in therapy-naive (less than or equal to 56 days of antiretroviral therapy) pediatric subjects are listed in Table 5.

**Table 5. Selected Clinical Adverse Reactions and Physical Findings (Greater than or Equal to 5% Frequency) in Pediatric Subjects in Trial ACTG 300**

| Adverse Reaction | EPIVIR 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 (less than or equal to 56 days of antiretroviral therapy) pediatric subjects are listed in Table 6.

**Table 6. Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Subjects in Trial ACTG 300**

| Test (Abnormal Level) | EPIVIR plus Zidovudine | Didanosine |
|---|---|---|
| Neutropenia (ANC<400 cells/$mm^3$) | 8% | 3% |
| Anemia (Hgb<7 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 subjects receiving zidovudine 180 mg per $m^2$ every 6 hours in open-label trials. Additionally, adverse reactions reported at an incidence of less than 6% in these trials 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 oral solution at 2 mg per kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse reactions were anemia (hemoglobin less than 9 g per dL) and neutropenia (less than 1,000 cells per mm3). 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 g per dL for neonates receiving zidovudine compared with 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 in neonates 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.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of zidovudine. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Body as a Whole:* Back pain, chest pain, flu-like syndrome, generalized pain, redistribution/accumulation of body fat *[see Warnings and Precautions (5.8)]*.

*Cardiovascular:* Cardiomyopathy, syncope.

*Eye:* Macular edema.

*Gastrointestinal:* Constipation, dysphagia, flatulence, oral mucosa pigmentation, mouth ulcer.

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

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

*Hepatobiliary:* 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.

*Reproductive System and Breast: Gynecomastia.*

*Respiratory:* Dyspnea, rhinitis, sinusitis.

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

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

*Renal and Urinary:* 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

Teratogenic Effects

*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 *[see Clinical Studies (14.3)]*. 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 *[see Clinical Studies (14.3)]*. 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 per 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. 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.

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States 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 subjects aged at least 6 weeks 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 (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.2, 14.3)]*.

### 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

Unchanged zidovudine and its glucuronide metabolite (formed in the liver) are primarily eliminated from the body by renal excretion. In patients with severely impaired renal function (CrCl less than 15 mL per min), dosage reduction is recommended *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

### 8.7 Hepatic Impairment

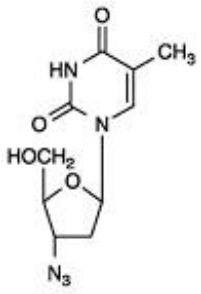
Zidovudine is primarily eliminated by hepatic metabolism and zidovudine concentrations appear to be increased in patients with impaired hepatic function, which may increase the risk of hematologic toxicity. Frequent monitoring of hematologic toxicities is advised. There are insufficient data to recommend dose adjustment of zidovudine in patients with impaired hepatic function or liver cirrhosis *[see Dosage and Administration (2.6), 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. 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. If overdose occurs, the patient should be monitored for evidence of toxicity and given standard supportive treatment as required.

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

Zidovudine Syrup (Zidovudine Oral Solution, USP) is for oral administration. Each (mL) of zidovudine oral solution contains 10 mg of zidovudine and the inactive ingredients sodium benzoate 0.2% (added as a preservative), citric acid anhydrous, strawberry cream flavor, glycerin, and sucrose.

Meets USP Organic Impurities Procedure 2

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.3 Pharmacokinetics

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 oral solution compared with zidovudine capsules. The pharmacokinetic properties of zidovudine in fasting adult subjects are summarized in Table 7.

**Table 7. Zidovudine Pharmacokinetic Parameters in Adult Subjects**

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

[a]Median [range] for 50 paired samples drawn 1 to 8 hours after the last dose in subjects on chronic therapy with zidovudine.
[b]Approximate range.

Distribution

The apparent volume of distribution of zidovudine, is 1.6 ± 0.6 L per kg (Table 7); and binding to plasma protein is low (less than 38%).

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 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 per kg every 8 hours to 10 mg per 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 subjects with impaired renal function (n = 14) following a single 200 mg oral dose (Table 8). Plasma concentrations of AMT were not determined. No dose adjustment is recommended for patients with CrCl greater than or equal to 15 mL per min.

**Table 8. Zidovudine Pharmacokinetic Parameters in Subjects with Severe Renal Impairment[a]**

| Parameter | Control Subjects (Normal Renal Function) (n = 6) | Subjects with Renal Impairment (n = 14) |
|---|---|---|
| CrCl (mL/min) | 120 ± 8 | 18 ± 2 |
| Zidovudine AUC (ng•h/mL) | 1,400 ± 200 | 3,100 ± 300 |
| Zidovudine half-life (h) | 1 ± 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 trial in subjects undergoing hemodialysis (n = 5) or peritoneal dialysis (n = 6) receiving escalating oral 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 subjects 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 (2.5)]*.

*Hepatic Impairment:* Data describing the effect of hepatic impairment on the pharmacokinetics of

zidovudine are limited. However, zidovudine is eliminated primarily by hepatic metabolism, and it appears that zidovudine clearance is decreased and plasma concentrations are increased in subjects with hepatic impairment. There are insufficient data to recommend dose adjustment of zidovudine in patients with impaired hepatic function or liver cirrhosis *[see Dosage and Administration (2.6)]*.

*Pediatric Patients:* Zidovudine pharmacokinetics have been evaluated in HIV-1-infected pediatric subjects (Table 9).

*Patients Aged 3 Months to 12 Years:* Overall, zidovudine pharmacokinetics in pediatric patients older than 3 months 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 per $m^2$ every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult subjects, the major route of elimination was by metabolism to GZDV. After IV 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 (2.2)]*.

*Patients Aged Less than 3 Months:* Zidovudine pharmacokinetics have been evaluated in pediatric subjects 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 ± 5.8 hours. In neonates less than or equal to 14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric subjects older than 14 days. For dose recommendations for neonates *[see Dosage and Administration (2.3)]*.

**Table 9. Zidovudine Pharmacokinetic Parameters in Pediatric Subjects[a]**

| Parameter | Birth to 14 Days | Aged 14 Days to 3 Months | Aged 3 Months to 12 Years |
|---|---|---|---|
| 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][b] (n = 38) |
| CL (L/h/kg) | 0.65 ± 0.29 (n = 18) | 1.14 ± 0.24 (n = 16) | 1.85 ± 0.47 (n = 20) |
| Elimination half-life (h) | 3.1 ± 1.2 (n = 21) | 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 trial 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.

*Geriatric Patients:* Zidovudine pharmacokinetics have not been studied in subjects over 65 years of age.

*Gender:* A pharmacokinetic trial 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 10. 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 Oral Dose | n | Zidovudine Concentrations | | Concentration of Coadministered Drug |
| | | | AUC | Variability | |
| Atovaquone 750 mg every 12 h with food | 200 mg every 8 h | 14 | ↑AUC 31% | Range: 23% to 78%[b] | ↔ |
| Clarithromycin 500 mg twice daily | 100 mg every 4 h x 7 days | 4 | ↓AUC 12% | Range: ↓34% to ↑14%[b] | Not Reported |
| Fluconazole 400 mg daily | 200 mg every 8 h | 12 | ↑AUC 74% | 95% CI: 54% to 98% | Not Reported |
| Lamivudine 300 mg every 12 h | single 200 mg | 12 | ↑AUC 13% | 90% CI: 2% to 27% | ↔ |
| Methadone 30 to 90 mg daily | 200 mg every 4 h | 9 | ↑AUC 43% | Range: 16% to 64%[b] | ↔ |
| Nelfinavir 750 mg every 8 h x 7 to 10 days | single 200 mg | 11 | ↓AUC 35% | Range: 28% to 41%[b] | ↔ |
| Probenecid 500 mg every 6 h x 2 days | 2 mg/kg every 8 h x 3 days | 3 | ↑AUC 106% | Range 100% to 170%[b] | Not Assessed |
| Rifampin 600 mg daily x 14 days | 200 mg q 8 h x 14 days | 8 | ↓AUC 47% | 90% CI: 41% to 53% | Not Assessed |
| Ritonavir 300 mg every 6 h x 4 days | 200 mg every 8 h x 4 days | 9 | ↓AUC 25% | 95% CI: 15% to 34% | ↔ |
| Valproic acid 250 mg or 500 mg every 8 h x 4 days | 100 mg every 8 h 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 trial 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 subjects *[see Warnings and Precautions (5.5)]*.

**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 per 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 subjects 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 subjects 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 trial of 167 HIV-1-infected subjects, isolates (n = 2) with multi-drug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from subjects treated for at least 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

Carcinogenesis

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 per kg per day in mice and 80, 220, and 600 mg per kg per day in rats. The doses in mice were reduced to 20, 30, and 40 mg per kg per day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg per kg per day on Day 91 and then to 300 mg per kg per 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.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg per kg per day or 40 mg per kg per 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 per day or 25 mg per day ( approximately 1,000 mg per kg nonpregnant body weight or approximately 450 mg per 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.

Mutagenesis

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.

Impairment of Fertility

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.

### 13.2 Animal Toxicology and/or Pharmacology

Oral teratology studies in the rat and in the rabbit at doses up to 500 mg per kg per 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 per kg per day and rabbits given 500 mg per kg per 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 per kg per day (very near the oral median lethal dose in rats of 3,683 mg per 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 per day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg per kg per 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 trial ACTG 320. This trial was a multi-center, randomized, double-blind, placebo-controlled trial that compared zidovudine 600 mg per day plus EPIVIR 300 mg per day with zidovudine plus EPIVIR plus indinavir 800 mg three times daily. 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 trials of treatment-naive subjects 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 trials enrolled subjects with advanced disease (BW 002), and asymptomatic or mildly symptomatic disease in subjects with CD4+ cell counts between 200 and 500 cells per $mm^3$ (ACTG 016 and ACTG 019). A survival benefit for monotherapy with zidovudine was not demonstrated in the latter 2 trials. Subsequent trials showed that the clinical benefit of monotherapy with zidovudine was time limited.

### 14.2 Pediatric Patients

ACTG 300 was a multi-center, randomized, double-blind trial that provided for comparison of EPIVIR plus zidovudine to didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive pediatric subjects were enrolled in these 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), the mean baseline CD4+ cell count was 868 cells per $mm^3$, and the mean baseline plasma HIV-1 RNA was 5 $log_{10}$ copies per mL. The median duration that subjects remained on trial was approximately 10 months. Results are summarized in Table 11.

**Table 11. Number of Subjects (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)**

| Endpoint | EPIVIR plus Zidovudine (n = 236) | Didanosine (n = 235) |
|---|---|---|
| HIV 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%) |

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

The utility of zidovudine for the prevention of maternal-fetal HIV-1 transmission was demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG 076) conducted in HIV-1-infected pregnant women with CD4+ cell counts of 200 to 1,818 cells per $mm^3$ (median in the treated group: 560 cells per $mm^3$) who had little or no previous exposure to zidovudine. Oral zidovudine was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by IV administration of zidovudine during labor and delivery. Following birth, neonates received oral zidovudine solution for 6 weeks. The trial showed a statistically significant difference in the incidence of HIV-1 infection in the neonates (based on viral culture from peripheral blood) between the group receiving zidovudine and the group receiving placebo. Of 363 neonates evaluated in the trial, the estimated risk of HIV-1 infection was 7.8% in the group receiving zidovudine and 24.9% in the placebo group, a relative reduction in transmission risk of 68.7%. Zidovudine was well tolerated by mothers and infants. There was no

difference in pregnancy-related adverse events between the treatment groups.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

**Zidovudine Syrup (Zidovudine Oral Solution, USP), 10 mg/mL** is (colorless to pale yellow, strawberry-flavored) containing 10 mg zidovudine in each (mL).

| | |
|---|---|
| Bottle of 240 mL | NDC 65862-048-24 |

**Store at** 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Inform patients that potentially life-threatening hypersensitivity reactions (e.g., anaphylaxis, Stevens-Johnson syndrome) can occur while receiving zidovudine. Instruct patients to immediately contact their healthcare provider if they develop rash, as it may be a sign of a more serious reaction. Advise patients that it is very important that they remain under a healthcare provider's care during treatment with zidovudine.

Neutropenia and Anemia

Inform Patients 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. Advise patients that if toxicity develops, they may require transfusions or drug discontinuation. Advise patients 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

Inform patients 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 (5.3)]*.

Lactic Acidosis/Hepatomegaly

Inform patients 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 (5.4)]*.

HIV-1/HCV Co-infection

Inform patients with HIV-1/HCV co-infection 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 (5.5)]*.

Use with Other Zidovudine-containing Products

Zidovudine should not be administered with combination products that contain zidovudine as one of their components (e.g., COMBIVIR [lamivudine and zidovudine] tablets or TRIZIVIR [abacavir sulfate, lamivudine, and zidovudine] tablets) *[see Warnings and Precautions (5.6)]*.

Immune Reconstitution Syndrome

In some patients with advanced HIV infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Advise patients to inform their healthcare provider immediately of any symptoms of infection *[see Warnings and Precautions (5.7)]*.

Redistribution/Accumulation of Body Fat

Inform patients 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 (5.8)]*.

Common Adverse Reactions

Inform patients 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

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

Pregnancy

Inform pregnant women considering the use of zidovudine during pregnancy for prevention of HIV-1 transmission to their infants 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)]*.

Advise HIV-1-infected pregnant women not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected *[see Use in Specific Populations (8.3)]*.

Information about HIV-1 Infection

Zidovudine is not a cure for HIV-1 infection, and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients must remain on continuous HIV therapy to control HIV-1 infection and decrease HIV-1-related illness. Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician when using zidovudine.

Patients should be informed to take all HIV medications exactly as prescribed.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- Continue to practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- Female patients should be advised not to breastfeed.Zidovudine is excreted in human breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Instruct patients that if they miss a dose, they should just take their next dose at the usual time. Patients should not double their next dose.

COMBIVIR, EPIVIR, and TRIZIVIR are registered trademarks of the ViiV Healthcare group of companies.

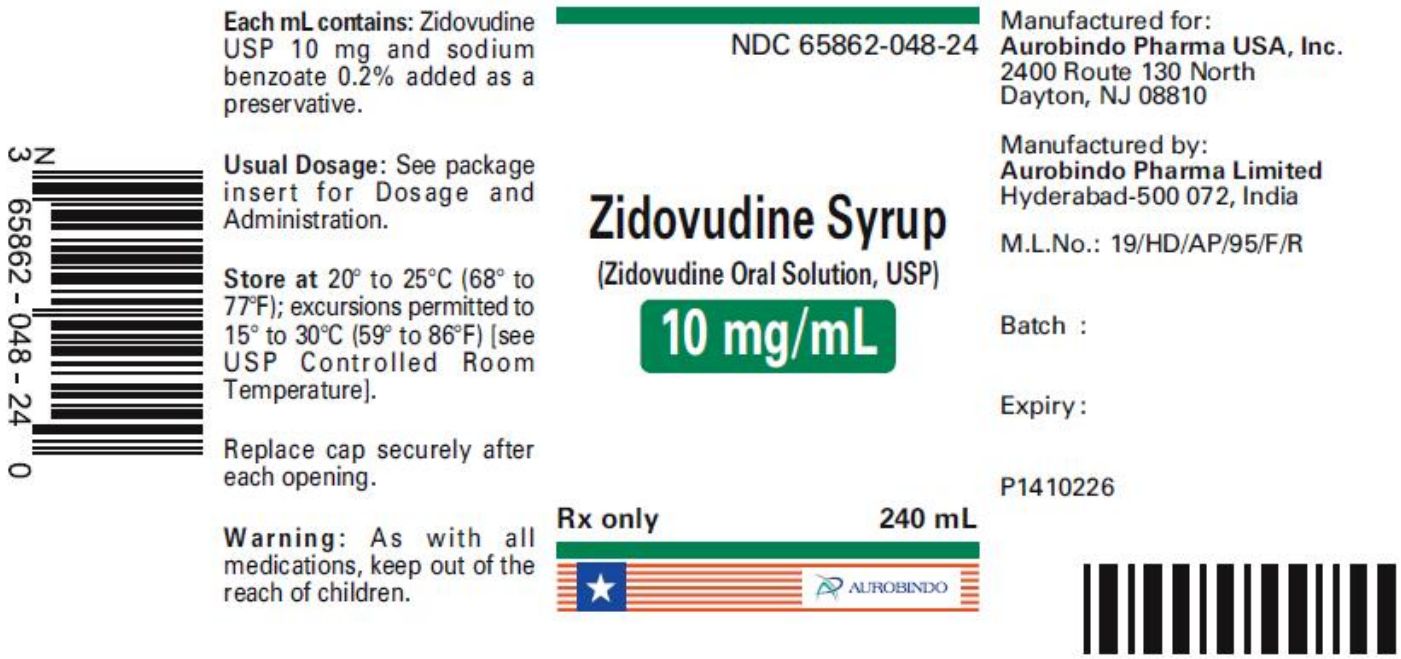
Manufactured for:
**Aurobindo Pharma USA, Inc.**
2400 Route 130 North
Dayton, NJ 08810

Manufactured by:
**Aurobindo Pharma Limited**
Hyderabad–500 072, India

Revised: 02/2015

**PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 10 mg/mL (240 mL Bottle)**

**NDC 65862-048-24**
**Zidovudine Syrup**
**(Zidovudine Oral Solution, USP)**
**10 mg/mL**
**Rx only 240 mL**
**AUROBINDO**




# ZIDOVUDINE

zidovudine syrup

## Product Information

| | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:65862-048 |
| **Route of Administration** | ORAL | | |

## Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|---|---|
| **ZIDOVUDINE** (UNII: 4B9XT59T7S) (ZIDOVUDINE - UNII:4B9XT59T7S) | ZIDOVUDINE | 10 mg in 1 mL |

## Inactive Ingredients

| Ingredient Name | Strength |
|---|---|
| **SODIUM BENZOATE** (UNII: OJ245FE5EU) | |
| **ANHYDROUS CITRIC ACID** (UNII: XF417D3PSL) | |
| **GLYCERIN** (UNII: PDC6A3C0OX) | |
| **SUCROSE** (UNII: C151H8M554) | |

## Product Characteristics

| | | | |
|---|---|---|---|
| **Color** | YELLOW (Colourless to Pale Yellow) | **Score** | |
| **Shape** | | **Size** | |
| **Flavor** | STRAWBERRY (Strawberry Cream) | **Imprint Code** | |
| **Contains** | | | |

## Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| 1 | NDC:65862-048-24 | 240 mL in 1 BOTTLE; Type 0: Not a Combination Product | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| ANDA | ANDA077268 | 09/19/2005 | |

## Labeler - Aurobindo Pharma Limited (650082092)

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| Aurobindo Pharma Limited | | 918917642 | ANALYSIS(65862-048) , MANUFACTURE(65862-048) |

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| Aurobindo Pharma Limited | | 918917662 | API MANUFACTURE(65862-048) |

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| Aurobindo Pharma Limited | | 918917626 | API MANUFACTURE(65862-048) |

Revised: 9/2015 Aurobindo Pharma Limited