PRODUCT MONOGRAPH

NOVO-AZT

(Zidovudine)

100 mg Capsules

Antiretroviral Agent

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THERAPEUTIC CLASSIFICATION

Antiretroviral Agent

ACTION AND CLINICAL PHARMACOLOGY

NOVO-AZT (zidovudine) is a potent inhibitor of the *in vitro* replication of some retroviruses including human immunodeficiency virus, HIV. Zidovudine is a thymidine analogue in which the 3-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Cellular thymidine kinase converts zidovudine into zidovudine monophosphate. The monophosphate is further converted into the diphosphate by cellular thymidylate kinase and to the triphosphate derivative by other cellular enzymes. Zidovudine triphosphate interferes with the HIV viral RNA dependent DNA polymerase (reverse transcriptase) and thus inhibits viral replication. Zidovudine triphosphate also inhibits cellular α-DNA polymerase, but at concentrations 100-fold higher than those required to inhibit reverse transcriptase. *In vitro,* zidovudine triphosphate has been shown to be incorporated into growing chains of DNA by viral reverse transcriptase. When incorporation by the viral enzyme occurs, the DNA chain is terminated. Studies in cell culture suggest that zidovudine incorporation by cellular α-DNA polymerase may occur, but only to a very small extent and not in all test systems. Cellular γ-DNA polymerase shows some sensitivity to inhibition by the zidovudine triphosphate with 50% inhibitory concentration (IC_{50}) values 400 to 900 times greater than that for HIV reverse transcriptase.

After oral dosing in adults, zidovudine is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours, with an average oral bioavailability of 65%. In pediatric patients older than 3 months, the pharmacokinetics of zidovudine are similar to those in adult patients.

Bioavailability

A two-way, single dose, crossover study was performed to evaluate the comparative bioavailability of NOVO-AZT 100 mg capsules with Retrovir® 100 mg capsules, under fasting conditions. The pharmacokinetic data calculated for zidovudine in the NOVO-AZT and Retrovir® capsule formulations are tabulated below:

Table 1
TABLE OF COMPARATIVE BIOAVAILABILITY DATA
NOVO-AZT CAPSULES
(2 x 100 mg)

Parameters	NOVO-AZT	RETROVIR®	Ratio of Geometric Means (%)
AUC_T* (ng•h/mL)	1224 (4)	1141 (4)	107
AUC_I* (ng•h/mL)	1261 (4)	1176 (4)	107
C_{max}* (ng/mL)	829 (6)	692 (8)	120
T_{max}+ (h)	0.93 ± 0.56	0.83 ± 0.30	-
$T_{½}$+ (h)	1.14 ± 0.58	1.08 ± 0.49	-

* Geometric means (CV)
+Arithmetic means (SD)

INDICATIONS AND CLINICAL USE

NOVO-AZT (zidovudine) is indicated for the treatment of HIV infection when antiretroviral therapy is warranted.

The duration of clinical benefit from antiretroviral therapy may be limited. Alterations in antiretroviral therapy should be considered if disease progression occurs during treatment.

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

Zidovudine in combination with certain antiretroviral agents has been shown to be superior to monotherapy in one or more of the following: delaying death, delaying development of AIDS, increasing CD4 cell counts, and decreasing plasma HIV RNA. Use of zidovudine in some combinations is based on surrogate marker data. The complete prescribing information for each drug should be consulted before combination therapy which includes NOVO-AZT is initiated.

Maternal-Fetal HIV Transmission

NOVO-AZT is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral NOVO-AZT beginning between 14 and 34 weeks of gestation, intravenous zidovudine during labor, and administration of zidovudine Syrup to the newborn after birth (see AVAILABILITY OF DOSAGE FORMS). However, transmission to infants may still occur in some cases despite the use of this regimen. The efficacy of this regimen for preventing HIV transmission in women who have received zidovudine for a prolonged period before pregnancy has not been evaluated. The safety of zidovudine for the mother or fetus during the first trimester of pregnancy has not been assessed.

The utility of zidovudine for the prevention of maternal-fetal HIV transmission was demonstrated in a randomized, double-blind, placebo-controlled trial (ACTG 076) conducted in HIV-infected pregnant women who had little or no previous exposure to zidovudine and CD4 cell counts of 200 to 1818 cells/mm^3 (median in the treated group: 560 cells/mm^3). Oral zidovudine was initiated between 14 and 34 weeks of gestation (median 11 weeks of therapy) followed by intravenous administration of zidovudine during labor and delivery. After birth, infants received oral zidovudine syrup for 6 weeks. The study showed a statistically significant difference in the incidence of HIV infection in the infants (based on viral culture from peripheral blood) between the group receiving zidovudine and the group receiving placebo. Of 363 infants evaluated in the study, the estimated risk of HIV infection was 8.3% in the group receiving zidovudine and 25.5% in the placebo group, a relative reduction in transmission risk of 67.5%.

Zidovudine was well tolerated by mothers and infants. There was no difference in pregnancy-related adverse events between the treatment groups. The mean difference in hemoglobin values was less than 1.0 g/dL for infants receiving zidovudine compared to infants receiving placebo. Infants did not require transfusion and hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with zidovudine. The long-term consequences of *in utero* and infant exposure to zidovudine are unknown.

CONTRAINDICATIONS

NOVO-AZT (zidovudine) is contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulations.

WARNINGS

Bone Marrow Suppression

NOVO-AZT (zidovudine) should be used with extreme caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm^3 or hemoglobin <9.5 g/dL. In all of the placebo-controlled studies, but most frequently in patients with advanced symptomatic disease, anemia and granulocytopenia were the most significant adverse events observed (see ADVERSE REACTIONS). There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuation of the drug.

Myopathy

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

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Rare occurrences of lactic acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported with the use of antiretroviral nucleoside analogues, including zidovudine and zalcitabine, and are potentially fatal; it is not known whether these events are causally related to the use of these drugs. Lactic acidosis should be considered whenever a patient receiving therapy with NOVO-AZT develops unexplained tachypnea, dyspnea, or fall in serum bicarbonate level. Under these circumstances, therapy with NOVO-AZT should be suspended until the diagnosis of lactic acidosis has been excluded. Caution should be exercised when administering NOVO-AZT to any patient, particularly obese women, with hepatomegaly, hepatitis, or other known risk factors for liver disease. These patients should be followed closely while on therapy with NOVO-AZT. The significance of elevated aminotransferase levels (suggesting hepatic injury) in HIV-infected patients prior to starting zidovudine or while on zidovudine is unclear. Treatment with NOVO-AZT should be suspended in the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly, or metabolic/lactic acidosis of unknown etiology.

Other Serious Adverse Reactions

Several serious adverse events have been reported with use of zidovudine in clinical practice. Reports of pancreatitis, sensitization reactions (including anaphylaxis in one patient), vasculitis, and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. Changes in skin and nail pigmentation have been associated with the use of zidovudine.

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated (see DRUG INTERACTIONS under PRECAUTIONS).

Before combination therapy with NOVO-AZT is initiated, consult the complete prescribing information for each drug. The safety profile of zidovudine plus other antiretroviral agents reflects the individual safety profiles of each component.

The incidence of adverse reactions appears to increase with disease progression, and patients should be monitored carefully, especially as disease progression occurs.

PRECAUTIONS

General

Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function, dosage reduction is recommended (see PHARMACOLOGY and DOSAGE AND ADMINISTRATION). Although very little data are available, patients with severely impaired hepatic function may be at greater risk of toxicity.

Very rare occurrences of pure red cell aplasia have been reported with zidovudine use. Discontinuation of zidovudine has resulted in normalization of hematological parameters in patients with suspected zidovudine-induced pure red cell aplasia.

Use in Infancy

A positive test for HIV-antibody in children under 15 months of age may represent passively acquired maternal antibodies, rather than an active antibody response to infection in the infant. Thus, the presence of HIV-antibody in a child less than 15 months of age must be interpreted with caution, especially in the asymptomatic infant. Auxiliary diagnostic tests may be required to confirm infection in such children.

Use in Children

See INDICATIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections. The pharmacokinetics of zidovudine in pediatric patients greater than 3 months of age is similar to that of zidovudine in adult patients.

Use in Pregnancy

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

Pregnant women considering the use of zidovudine during pregnancy for prevention of HIV-transmission to their infants should be advised that transmission may still occur in some cases despite therapy. The long-term consequences of *in utero* and infant exposure to zidovudine are unknown. The long-term effects of early or short-term use of zidovudine in pregnant women are also unknown.

Antiretroviral Pregnancy Registry

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

Nursing Mothers

It is not known whether zidovudine is excreted in human milk or whether zidovudine reduces the potential for transmission of HIV in breast milk. Lactating mice administered zidovudine (200 mg/kg intraperitoneally) were found to have milk concentrations of zidovudine five times the corresponding serum zidovudine concentration. Milk concentrations of zidovudine declined at a slower rate than serum zidovudine concentrations.

It is advisable to caution mothers against breast-feeding to avoid postnatal transmission of HIV to a child who may not yet be infected.

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.

Drug Interactions

Ganciclovir

Use of zidovudine in combination with ganciclovir increases the risk of hematologic toxicities in some patients with advanced HIV disease. Should the use of this combination become necessary in the treatment of patients with HIV disease, dose reduction or interruption of one or both agents may be necessary to minimize hematologic toxicity. Hematologic parameters, including hemoglobin, hematocrit, and white blood cell count with differential, should be monitored frequently in all patients receiving this combination.

Interferon-alpha

Hematologic toxicities have also been seen when zidovudine is used concomitantly with interferon-alpha. As with the concomitant use of zidovudine and ganciclovir, dose reduction or interruption of one or both agents may be necessary, and hematologic parameters should be monitored frequently.

Bone Marrow Suppressive Agents/Cytotoxic Agents

Coadministration of zidovudine with drugs that are cytotoxic or which interfere with RBC/WBC number or function (e.g. dapsone, flucytosine, vincristine, vinblastine, or adriamycin) may increase the risk of hematologic toxicity.

Probenecid

Limited data suggest that probenecid may increase zidovudine levels by inhibiting glucuronidation and/or reducing renal excretion of zidovudine. Some patients who have used zidovudine concomitantly with probenecid have developed flu-like symptoms consisting of myalgia, malaise, and/or fever and maculopapular rash.

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-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.

Methadone

In a pharmacokinetic study of nine HIV-positive patients receiving methadone-maintenance (30 to 90 mg daily) concurrent with 200 mg of zidovudine every 4 hours, no changes were observed in the pharmacokinetics of methadone upon initiation of therapy with zidovudine and after 14 days of treatment with zidovudine. No adjustments in methadone-maintenance requirements were reported. However, plasma levels of zidovudine were elevated in some patients while remaining unchanged in others. The exact mechanism and clinical significance of these data are unknown.

Fluconazole

Preliminary data suggest that fluconazole interferes with the oral clearance and metabolism of zidovudine. In a pharmacokinetic interaction study in which 12 HIV-positive men received zidovudine alone and in combination with fluconazole, increases in the mean peak serum concentration (79%), AUC (70%) and half-life (38%) were observed at steady state. The clinical significance of this interaction is unknown.

Atovaquone

Data from 14 HIV-infected volunteers who were given atovaquone tablets 750 mg every 12 hours with zidovudine 200 mg every 8 hours showed a 24% ± 12% decrease of zidovudine oral clearance, leading to a 35% ± 23% increase in plasma zidovudine AUC. The glucoronide metabolite:parent ratio decreased from a mean of 4.5 when zidovudine was administered alone to 3.1 when zidovudine was administered with atovaquone tablets. Zidovudine had no effect on atovaquone pharmacokinetics.

Valproic Acid

The concomitant administration of valproic acid 250 mg (n=5) or 500 mg (n=1) every 8 hours and zidovudine 100 mg orally every 8 hours for 4 days to six HIV-infected, asymptomatic male volunteers resulted in a 79% ± 61% (mean ± SD) increase in the plasma zidovudine AUC and a 22% ± 10% decrease in the plasma GZDV AUC as compared to the administration of zidovudine in the absence of valproic acid. The GZDV/zidovudine urinary excretion ratio decreased 58% ± 12%. Because no change in the zidovudine plasma half-life occurred, these results suggest that valproic acid may increase the oral bioavailability of zidovudine through inhibition of first-pass metabolism. Although the clinical signification of this interaction is unknown, patients should be monitored more closely for a possible increase in zidovudine-related adverse effects. The effect of zidovudine on the pharmacokinetics of valproic acid was not evaluated.

Lamivudine

Zidovudine and lamivudine were coadministered to 12 asymptomatic HIV-positive patients in a single-center, open-label, randomized, crossover study. No significant differences were observed in AUC_{∞} or total clearance for lamivudine or zidovudine when the two drugs were administered together. Coadministration of zidovudine with lamivudine resulted in an increase of 39% ± 62% (mean ± SD) in Cmax of zidovudine.

Other Agents

Some drugs such as trimethoprim-sulfamethoxazole, pyrimethamine, and acyclovir may be necessary for the management or prevention of opportunistic infections. In the placebo-controlled trial in patients with advanced HIV disease, increased toxicity was not detected with limited exposure to these drugs. However, there is one published report of neurotoxicity (profound lethargy) associated with concomitant use of zidovudine and acyclovir.

Preliminary data from a drug interaction study (n=10) suggest that coadministration of 200 mg zidovudine and 600 mg rifampin decreases the area under the zidovudine plasma concentration curve by an average of 48% ± 34%. However, the effect of once daily dosing of rifampin on multiple daily doses of zidovudine is unknown. In vitro, combinations of zidovudine with either ribavirin or stavudine are antagonistic. The concomitant use of either ribavirin or stavudine with zidovudine should be avoided.

INFORMATION FOR PATIENTS

The patient should be counselled about the use of NOVO-AZT. The following text is a guideline.

NOVO-AZT (zidovudine) is prescribed to slow down the effects of the HIV virus; it is not a cure. Illnesses associated with HIV infection, including other infections, may still happen. Therefore, it is very important to keep appointments with your doctor and to report any change in your health as it occurs.

Zidovudine has been extensively studied in humans for limited periods of time. Studies have shown that treatment will benefit your health. However, the effectiveness and overall safety of zidovudine is unknown beyond the length of time for which it has been studied.

The effectiveness and overall safety of zidovudine in women, intravenous drug users, and ethnic minorities are not different than that observed in white males.

An important but reversible side-effect of zidovudine, particularly in patients with more severe disease, can be a fall in the number of red blood cells (which carry oxygen) and a reduction in the number of white blood cells (which fight infection). Since a reduction in these cells can directly affect your health, it is important to have your blood tested as often as your doctor requests it. In some cases, it may be necessary to adjust the dose of the drug, temporarily discontinue the drug, give a blood transfusion, or stop the drug altogether.

It is important to understand that although these blood effects can occur at any stage, they are much more common in more advanced disease and in patients who start zidovudine therapy late in their illness.

Other side-effects of zidovudine include nausea and vomiting. Contact your doctor if you experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis (which your physician can explain to you) or any other unexpected adverse events while being treated with NOVO-AZT.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breasts and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

An additional precaution is that some other drugs may change the usefulness and safety of NOVO-AZT. It is therefore very important that you tell your doctor about all the drugs you are taking. Ask your doctor before you decide to take any new drugs, even if these are available without a prescription.

It is also important to take NOVO-AZT exactly as prescribed. Altering the dose without the direct advice of your physician is unwise, as is sharing your medication with others.

For pregnant women who are considering the use of NOVO-AZT during pregnancy for the prevention of HIV-transmission to their infants, it is important to understand that transmission may still occur in some cases (about 8%) despite using zidovudine. The long-term safety in treated fetuses, neonates, or infants has not been established.

HIV-infected women should not breast-feed in order to prevent transmission of HIV to a child who may not yet be infected.

HIV is usually spread by sexual contact or by contaminated needles. This risk still exists during NOVO-AZT therapy; thus, the practice of 'safe sex' and avoidance of sharing needles is imperative.

For patients receiving combination therapy with NOVO-AZT and zalcitabine, it is important to understand that the major toxicity of zalcitabine is peripheral neuropathy. Pancreatitis is another serious and potentially life-threatening toxicity that has been reported in less than 1% of patients treated with zalcitabine alone. Symptoms of peripheral neuropathy include tingling, burning, pain, or numbness in the hands or feet. Symptoms of pancreatitis include abdominal pain, and nausea and vomiting. These symptoms should be promptly reported to your physician. Since the development of peripheral neuropathy seems to be dose-related to zalcitabine, you should follow your physician's instructions regarding the prescribed dose. The long-term effects of zalcitabine in combination with NOVO-AZT are presently unknown. If you are a female of child-bearing age, you should use effective contraception while using zalcitabine.

ADVERSE REACTIONS

Adults

The frequency and severity of adverse events associated with the use of zidovudine in adults are greater in patients with more advanced infection at the time of initiation of therapy.

Anemia and Granulocytopenia

In all of the placebo-controlled studies, but most frequently in patients with advanced symptomatic HIV disease, anemia and granulocytopenia were the most significant adverse events observed.

Significant anemia most commonly occurred after 4 to 6 weeks of therapy and in many cases required dose adjustment, discontinuation of zidovudine, and/or blood transfusions. Frequent blood counts are strongly recommended in patients with advanced HIV disease taking NOVO-AZT. For asymptomatic HIV-infected individuals and patients with early HIV disease, most of whom have better marrow reserve, blood counts may be obtained less frequently, depending upon the patient's overall status. If anemia or granulocytopenia develops, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION).

The following table summarizes the relative incidence of hematologic adverse events observed in clinical studies by severity of HIV disease present at the start of treatment:

Table 2

Asymptomatic HIV Infection Study (n=1338)	Granulocytopenia (<750 cells/mm^3)			Anemia (Hgb<8.0 g/dL)		
	Zidovudine		Placebo	Zidovudine		Placebo
	1500 mg/day*	500 mg/day		1500 mg/day*	500 mg/day	
CD4≤500	6.4% (n=457)	1.8%** (n=453)	1.6% (n=428)	6.4% (n=457)	1.1%** (n=453)	0.2% (n=428)

Early Symptomatic HIV Disease Study (n=713)	Granulocytopenia (<750 cells/mm^3)		Anemia (Hgb<8.0 g/dL)	
	Zidovudine 1200 mg/day*	Placebo	Zidovudine 1200 mg/day*	Placebo
CD4>200	4% (n=361)	1% (n=352)	4% (n=361)	0% (n=352)

Advanced Symptomatic HIV Disease Study (n=281)	Granulocytopenia (<750 cells/mm^3)		Anemia (Hgb<7.5g/dL)	
	Zidovudine 1500 mg/day*	Placebo	Zidovudine 1500 mg/day*	Placebo
CD4>200	10% (n=30)**	3% (n=30)	3% (n=30)**	0% (n=30)
CD4≤200	47% (n=114)	10% (n=107)	29% (n=114)	5% (n=107)

Advanced Symptomatic HIV Disease Dose Comparison Study (n=524)	Granulocytopenia (<750 cells/mm^3)		Anemia (Hgb<8.0 g/dL)	
	Zidovudine 1200 mg/day*	Zidovudine 600 mg/day	Zidovudine 1200 mg/day*	Zidovudine 600 mg/day
CD4≤200	(n=262) 51%	(n=262) 37%	(n=262) 39%	(n=262) 29%

* The currently recommended dose is 600 mg/day.

** Not statistically significant compared to placebo

Other Adverse Events (Advanced HIV Disease)

The anemia reported in patients with advanced HIV disease receiving zidovudine appeared to be the result of impaired erythrocyte maturation as evidenced by macrocytosis while on drug. Although mean platelet counts in patients receiving zidovudine were significantly increased compared to mean baseline values, thrombocytopenia did occur in some of these patients with advanced disease. Twelve percent of patients receiving zidovudine compared to 5% of patients receiving placebo had >50% decreases from baseline platelet count. Mild drug-associated elevations in total bilirubin levels have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection. The HIV-infected adults participating in these clinical trials often had baseline symptoms and signs of HIV disease and/or experienced adverse events at some time during the study. It was often difficult to distinguish adverse events possibly associated with administration of zidovudine from underlying signs of HIV disease or intercurrent illnesses.

The following table summarizes clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1500 mg/day of zidovudine in the original placebo-controlled study. Of the items listed in the table, only severe headache, nausea, insomnia and myalgia were reported at a significantly greater rate in patients receiving zidovudine.

Table 3

Percentage (%) of Patients with Clinical Events in the Advanced HIV Diseases Study		
Adverse Event	**Zidovudine 1500 mg/day* (n=144)%**	**Placebo (n=137)%**
BODY AS A WHOLE		
Asthenia	19	18
Diaphoresis	5	4
Fever	16	12
Headache	42	37
Malaise	8	7
GASTROINTESTINAL		
Anorexia	11	8
Diarrhea	12	18
Dyspepsia	5	4
GI pain	20	19
Nausea	46	18
Vomiting	6	3
MUSCULOSKELETAL		
Myalgia	8	241393158
NERVOUS		
Dizziness	6	
Insomnia	5	
Paresthesia	6	
Somnolence	8	
RESPIRATORY		
Dyspnea	5	
SKIN		
Rash	17	
SPECIAL SENSES		
Taste Perversion	5	

* The currently recommended dose is 600 mg daily.

Clinical adverse events which occurred in less than 5% of all adult patients treated with 1500 mg/day of zidovudine in the advanced HIV study are listed below. Since many of these adverse events were seen in placebo-treated patients as well as patients treated with zidovudine, their possible relationship to the drug is unknown.

Body as a whole:	Body odour, chills, edema of the lip, flu syndrome, hyperalgesia, back pain, chest pain, lymphadenopathy
Cardiovascular:	Vasodilation
Gastrointestinal:	Constipation, dysphagia, edema of the tongue, eructation, flatulence, bleeding gums, rectal hemorrhage, mouth ulcer
Musculoskeletal:	Arthralgia, muscle spasm, tremor, twitch
Nervous:	Anxiety, confusion, depression, emotional lability, nervousness, syncope, loss of mental acuity, vertigo
Respiratory:	Cough, epistaxis, pharyngitis, rhinitis, sinusitis, hoarseness
Skin:	Acne, pruritus, urticaria
Special senses:	Amblyopia, hearing loss, photophobia
Urogenital:	Dysuria, polyuria, urinary frequency, urinary hesitancy

Other Adverse Events (Early Symptomatic/Asymptomatic HIV Disease)

All events of a severe or life-threatening nature were monitored for adults in the placebo-controlled studies in early HIV disease and asymptomatic HIV infection. Data concerning the occurrence of additional signs or symptoms were also collected. No distinction was made between events possibly associated with the administration of the study medication and those due to the underlying disease. The following tables summarize all those events reported significantly more frequently by patients receiving zidovudine in these studies:

Table 4

Percentage (%) of Patients with Clinical Events in the Early Symptomatic HIV Disease Study		
Adverse Event	**Zidovudine 1200 mg/day* (n=361)%**	**Placebo (n=352)%**
BODY AS A WHOLE		
Asthenia	69	62
GASTROINTESTINAL		
Dyspepsia	6	1
Nausea	61	41
Vomiting	25	13

* The currently recommended dose is 600 mg daily.

Table 5

Percentage (%) of Patients with Clinical Events+ in an Asymptomatic HIV Infection Study			
Adverse Event	**Zidovudine 1500 mg/day* (n=457) %**	**Zidovudine 500 mg/day (n=453) %**	**Placebo (n=428) %**
BODY AS A WHOLE			
Asthenia	10.1	8.6†	5.8
Headache	58.0†	62.5	52.6
Malaise	55.6	53.2	44.9
GASTROINTESTINAL			
Anorexia	19.3	20.1	10.5
Constipation	8.1	6.4†	3.5
Nausea	57.3	51.4	29.9
Vomiting	16.4	17.2	9.8
NERVOUS			
Dizziness	20.8	17.9†	15.2

\+ Reported in ≥5% of study population
* The currently recommended dose is 600 mg/day.
† Not statistically significant versus placebo

Several serious adverse events have been reported with the use of zidovudine in clinical practice. Myopathy and myositis with pathological changes similar to that produced by HIV disease have been associated with prolonged use of zidovudine. Reports of hepatomegaly with steatosis, hepatitis, pancreatitis, lactic acidosis, sensitization reactions (including anaphylaxis in one patient), hyperbilirubinemia, vasculitis, and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. A single case of macular edema has been reported with the use of zidovudine. Changes in skin and nail pigmentation have been associated with the use of zidovudine (see WARNINGS).

Combination Therapy with Zidovudine and Zalcitabine

Only limited safety data are available on the combined use of zidovudine with zalcitabine. The major toxicities of zalcitabine are peripheral neuropathy and, less frequently, pancreatitis.

The following table includes clinical adverse events in the combination zalcitabine and zidovudine Protocol N3447/ACTG 106. Only eight patients were treated with the recommended combination regimen.

Table 6

Number and Percentage of Patients with Clinical Adverse Experiences Occurring in >3% of Patients Considered Possibly or Probably Related to Study Drug				
`HIVID' + ZDV Combination Trial Pooled Concomitant Regimens	**N3447/ACTG 106[a] No prior ZDV**			
	n=47 (%)			
Body System Adverse Event	**mild/mod/sev**		**mod/sev**	
Peripheral Neuropathy	12	(25.5)	2	(4.3)
Gastrointestinal				
Nausea	17	(36.2)	4	(8.5)
Oral Ulcers	13	(27.7)	2	(4.3)
Abdominal pain	10	(21.3)	4	(8.5)
Diarrhea	7	(14.9)	5	(10.6)
Vomiting	7	(14.9)	1	(2.1)
Anorexia	6	(12.8)	3	(6.4)
Constipation	3	(6.4)	1	(2.1)
Skin and Appendages				
Pruritus	7	(14.9)	2	(4.3)
Rash	7	(14.9)	1	(2.1)
Erythematous rash	3	(6.4)	1	(2.1)
Night sweats	3	(6.4)	1	(2.1)
Maculopapular rash	2	(4.3)	1	(2.1)
Follicular rash	2	(4.3)	0	(0.0)
Central and Peripheral NS				
Headache	18	(38.3)	4	(8.5)
Musculoskeletal				
Myalgia	7	(14.9)	1	(2.1)
Arthralgia	4	(8.5)	1	(2.1)
Body as a Whole				
Fatigue	16	(34.0)	4	(8.5)
Fever	7	(14.9)	1	(2.1)
Rigors	4	(8.5)	1	(2.1)
Chest pain	3	(6.4)	1	(2.1)
Weight decrease	3	(6.4)	2	(4.3)
Respiratory				
Pharyngitis	4	(8.5)	1	(2.1)

[a] Median duration of treatment ranged from 22 to 92 weeks among the arms.

Children

Anemia and Granulocytopenia

The incidences of anemia and granulocytopenia among children with advanced HIV disease receiving zidovudine occurred with similar incidence to that reported for adults with AIDS or advanced ARC (see above). The following table summarizes the occurrence of anemia (Hgb<7.5 g/dL) and granulocytopenia (<750 cells/mm^3) among 124 children receiving zidovudine for a mean of 267 days (range 3 to 855 days):

Table 7

	Granulocytopenia (<750 cells/mm^3)		Anemia (Hgb<7.5g/dL)	
	n	%	n	%
Advanced Pediatric HIV disease (n=124)	48	39	28*	23

* Twenty-two children received one or more transfusions due to a decline in hemoglobin to <7.5g/dL; an additional 15 children were transfused for hemoglobin levels >7.5 g/dL. Fifty-nine percent of the patients transfused had a pre-study history of anemia or transfusion requirement.

Management of neutropenia and anemia included, in some cases, dose modification and/or blood product transfusions. In the open-label studies, 17% had their dose modified (generally a reduction in dose by 30%) due to anemia, and 25% had their dose modified (temporary discontinuation or reduction by 30%) for neutropenia. Four children had zidovudine permanently discontinued because of neutropenia.

Macrocytosis was observed among the majority of children enrolled in the studies.

Other Adverse Events (Children)

The clinical adverse events reported among adult recipients of zidovudine may also occur in children.

In the open-label studies involving 124 children, 16 different clinical adverse events were reported by 24 children. No event was reported by more than 5.6% of the study populations. Due to the open-label design of the studies, it was difficult to determine possible events related to the use of zidovudine versus disease-related events. Therefore, all clinical events reported as associated with therapy with zidovudine or of unknown relationship to therapy with zidovudine are presented in the following table:

Table 8

Percentage (%) of Pediatric Patients with Clinical Events in Open-Label Studies		
Adverse Event	**n**	**%**
BODY AS A WHOLE		
Fever	4	3.2
Phlebitis*/Bacteremia	2	1.6
Headache	2	1.6
GASTROINTESTINAL		
Nausea	1	0.8
Vomiting	6	4.8
Abdominal Pain	4	3.2
Diarrhea	1	0.8
Weight Loss	1	0.8
NERVOUS		
Insomnia	3	2.4
Nervousness/Irritability	2	1.6
Decreased Reflexes	7	5.6
Seizure	1	0.8
CARDIOVASCULAR		
Left Ventricular Dilation	1	0.8
Cardiomyopathy	1	0.8
S_3 Gallop	1	0.8
Congestive Heart Failure	1	0.8
Generalized Edema	1	0.8
ECG Abnormality	3	2.4
UROGENITAL		
Hematuria/Viral Cystitis	1	0.8

* Peripheral vein I.V. catheter site

Use for the Prevention of Maternal-Fetal Transmission of HIV

In a randomized, double-blind, placebo-controlled trial in HIV-infected women and their infants conducted to determine the utility of zidovudine for the prevention of maternal-fetal HIV transmission, zidovudine syrup at 2 mg/kg was administered every 6 hours for 6 weeks to infants beginning within 12 hours after birth. The most commonly reported adverse experiences were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1000 cells/mm^3). Anemia occurred in 22% of the infants who received zidovudine and in 12% of the infants who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for infants receiving zidovudine compared to infants receiving placebo. No infants with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with zidovudine. Neutropenia was reported with similar frequency in the group that received zidovudine (21%) and in the group that received placebo (27%). The long-term consequences of *in utero* and infant exposure to zidovudine are unknown.

Post-Marketing Experience

The following events have been reported in patients treated with zidovudine without regard to causality. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. A reduction in dose or suspension of zidovudine therapy may be warranted in the management of these conditions.

Body as a whole: Redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution).

Hematological: Anaemia (which may require transfusions), neutropenia, leucopenia, aplastic anaemia, thrombocytopenia, pancytopenia (with marrow hypoplasia) and pure red cell aplasia.

Anemia, neutropenia, leucopenia and aplastic anemia occur more frequently at higher dosages (1200-1500mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD_4 cell counts less than $100/mm^3$. Dosage reduction or cessation of therapy may become necessary (see DOSAGE AND ADMINISTRATION). The incidence of neutropenia was also increased in those patients whose neutrophil counts, hemoglobin levels and serum vitamin B_{12} levels were low at the start of zidovudine therapy.

Liver/pancreas: raised blood levels of liver enzymes and bilirubin.

Gastrointestinal: Oral mucosa pigmentation.

Miscellaneous: Gynecomastia.

Skin: Sweating.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Cases of acute overdose in both children and adults have been reported with doses up to 50 grams. None were fatal.

The only consistent finding in these cases of overdose was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not severe. Some patients experienced nonspecific CNS symptoms such as headache, dizziness, drowsiness, lethargy, and confusion. One report of a grand mal seizure possibly attributable to zidovudine occurred in a 35-year-old male 3 hours after ingesting 36 grams of zidovudine. No other cause could be identified. 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, GZDV is enhanced.

Although no data are available, administration of activated charcoal may be used to aid in removal of unabsorbed drug.

DOSAGE AND ADMINISTRATION

Oral Administration

Adults

The recommended total oral daily dose of NOVO-AZT is 600 mg per day in divided doses in combination with other antiretroviral agents. The effectiveness of this dose compared to higher dosing regimens in improving the neurologic dysfunction associated with HIV disease is unknown. A small randomized study found a greater effect of higher doses of zidovudine on improvement of neurological symptoms in patients with pre-existing neurological disease.

Suggested dosing regimens are listed in the following table.

Table 9

Suggested Dosing Regimens

Formulation	Dosing Regimen
Capsules	three 100 mg NOVO-AZT Capsules every 12 hours or two 100 mg NOVO-AZT Capsules every 8 hours

Children

The recommended oral dose in children 3 months to 12 years of age is 180 mg/m^2 every 6 hours (720 mg/m^2 per day). This dose is equivalent to 1, 200 mg/day in adults. Do not exceed 200 mg for any individual dose.

Prevention of Maternal-Fetal HIV Transmission

The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their newborn infants is: (see AVAILABILITY OF DOSAGE FORMS)

Maternal Dosing

100 mg orally 5 times per day until the start of labor. During labor and delivery, intravenous zidovudine should be administered at 2 mg/kg (total body weight) over 1 hour followed by a continuous intravenous infusion at 1 mg/kg/h (total body weight) until clamping of the umbilical cord.

Infant Dosing

2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Infants unable to receive oral dosing may be administered zidovudine intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. See PRECAUTIONS if hepatic disease or renal insufficiency is present.

Monitoring of Patients

Hematologic toxicities appear to be related to pretreatment bone marrow reserve and to dose and duration of therapy. In patients with poor bone marrow reserve, particularly in patients with advanced symptomatic HIV disease, frequent monitoring of hematologic indices is recommended to detect serious anemia or granulocytopenia (see ADVERSE REACTIONS). In patients who experience hematologic toxicity, reduction in hemoglobin may occur as early as 2 to 4 weeks, and granulocytopenia usually occurs after 6 to 8 weeks.

Patients treated with zidovudine should be under close clinical observation to manage potential opportunistic infections associated with HIV disease. Prompt recognition of infection or toxicities and appropriate management is required.

Dose Adjustment

Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant granulocytopenia (granulocyte count of <750 cells/mm^3 or reduction of >50% from baseline) may require a dose interruption until evidence of marrow recovery is observed (see ADVERSE REACTIONS). In patients who develop significant anemia, dose modification does not necessarily eliminate the need for transfusion.

For less severe anemia or granulocytopenia, a reduction in daily dose may be adequate. If marrow recovery occurs following dose modification, gradual increases in dose may be appropriate depending on hematologic indices and patient tolerance.

In end-stage disease patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours for oral administration. (see Pharmacokinetics section of PHARMACOLOGY).

There are insufficient data to recommend dose adjustment of zidoduvine in patients with impaired hepatic function.

PHARMACEUTICAL INFORMATION

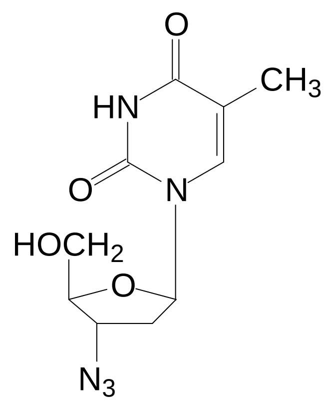
Drug Substance

Brand Name: NOVO-AZT

Common Name: Zidovudine

Chemical Name: 3'-azido-3'-deoxythymidine

Structural Formula:



Molecular Formula: $C_{10}H_{13}N_5O_4$

Molecular Weight: 267.24

Description: Zidovudine is a white to off-white, odourless, crystalline solid, sparingly soluble in water and freely soluble in methanol. The melting range is 118°C - 123°C.

COMPOSITION:

Each NOVO-AZT 100 mg Capsule contains 100 mg of zidovudine and the non-medicinal ingredients corn starch, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. The capsule imprinted with edible black ink, is made of titanium dioxide and gelatin.

STABILITY AND STORAGE RECOMMENDATIONS:

Store in white high density polyethylene bottles and unit dose packages between 15°C - 25°C and protect from light and moisture.

AVAILABILITY OF DOSAGE FORMS

NOVO-AZT (zidovudine) is available as:

100 mg -	Opaque white cap and opaque white body, hard gelatin capsule, printed ‘100’ and ‘novo’on opposing cap and body portions of the capsule and with a dark blue band on the cap,
Supplied:	In bottles of 100 and 500 and boxes of 100 as unit dose strips.

VIROLOGY

Zidovudine is an inhibitor of the *in vitro* replication of some retroviruses including HIV. This drug is a thymidine analogue in which the 3'-hydroxyl (-0H) group is replaced by an azido ($-N_3$) group. Cellular thymidine kinase converts zidovudine into zidovudine monophosphate. The monophosphate is further converted into the diphosphate by cellular thymidylate kinase and to the triphosphate derivative by other cellular enzymes. Zidovudine triphosphate interferes with the HIV viral RNA dependent DNA polymerase (reverse transcriptase) and thus inhibits viral replication. Zidovudine triphosphate also inhibits cellular α-DNA polymerase, but at concentrations 100-fold higher than those required to inhibit reverse transcriptase. *In vitro*, zidovudine triphosphate has been shown to be incorporated into growing chains of DNA by viral reverse transcriptase. When incorporation by the viral enzyme occurs, the DNA chain is terminated. Studies in cell culture suggest that zidovudine incorporation by cellular α-DNA polymerase may occur, but only to a very small extent and not in all test systems. Cellular γ-DNA polymerase shows some sensitivity to inhibition by the zidovudine triphosphate with 50% inhibitory concentration (IC_{50}) values 400 to 900 times greater than that for HIV reverse transcriptase.

***In Vitro* Activity**

The relationship between *in vitro* susceptibility of HIV to zidovudine and the inhibition of HIV replication in humans, or clinical response to therapy, has not been established. *In vitro* sensitivity results vary greatly depending upon the time between virus infection and zidovudine treatment of cell cultures, the particular assay used, the cell type employed, and the laboratory performing the test.

Zidovudine blocked 90% of detectable HIV replication *in vitro* at concentrations of $\leq$0.13 μg/mL

(ID_{90}) when added shortly after laboratory infection of susceptible cells. This level of antiviral effect was observed in experiments measuring reverse transcriptase activity in HIV-infected H9 cells, PHA stimulated peripheral blood lymphocytes, and unstimulated peripheral blood lymphocytes. The concentration of drug required to produce a 50% decrease in supernatant reverse transcriptase was 0.013 μg/mL (ID_{50}) in both HIV-infected H9 cells and peripheral blood lymphocytes. Zidovudine at concentrations of 0.13 μg/mL also provided >90% protection from a strain of HIV (HTLV IIIB) induced cytopathic effects in two tetanus-specific T_4 cell lines. HIV-p24 antigen expression was also undetectable at the same concentration in these cells. Partial inhibition of viral activity in cells with chronic HIV infection (presumed to carry integrated HIV DNA) required concentrations of zidovudine (8.8 μg/mL in one laboratory to 13.3 μg/mL in another) which are approximately 100 times as high as those necessary to block HIV replication in acutely infected cells. HIV isolates from 18 untreated individuals with AIDS or ARC had ID_{50} sensitivity values between 0.003 to 0.013 μg/mL and ID_{95} sensitivity values between 0.03 to 0.3 μg/mL.

Zidovudine, in its nonphosphorylated form, does not inhibit the reverse transcriptase activity associated with purified HIV virions. Zidovudine was equally active against American, Haitian, and African isolates of HIV.

Zidovudine has been shown to act additively or synergistically with a number of anti-HIV agents, including zalcitabine and interferon-alpha, and other agents such as acyclovir, lamivudine and didanosine in inhibiting the replication of HIV in cell culture.

The major metabolite of zidovudine,3'-azido-3'-deoxy-5'- *0*-β-*D*-glucopyranuronosyl-thymidine (GZDV), does not inhibit HIV replication *in vitro*. GZDV does not antagonize the antiviral effect of zidovudine *in vitro* nor does GZDV compete with zidovudine triphosphate as an inhibitor of HIV reverse transcriptase.

The cytotoxicity of zidovudine for various cell lines was determined using a cell growth inhibition assay. ID_{50} values for several human cell lines showed little growth inhibition by zidovudine except at concentrations >50 μg/mL. However, one human T-lymphocyte cell line was sensitive to the cytotoxic effect of zidovudine with an ID_{50} of 5 μg/mL. Moreover, in a colony-forming unit assay designed to assess the toxicity of zidovudine for human bone marrow, an ID_{50} value of <1.25 μg/mL was estimated. Two of 10 human lymphocyte cultures tested were found to be sensitive to zidovudine at 5 μg/mL or less.

Acyclovir (ACV) has been shown to potentiate zidovudine protection of T4 cells from HTLV IIIB-induced cytopathic effects. Zidovudine alone provided 50% protection from cytopathic effects (ED_{50}) at a concentration of 0.49 μg/mL. The ED_{50} decreased to 0.40 μg/mL in the presence of 0.5 μg/mL ACV and was further decreased to 0.22 μg/mL when the ACV concentration was increased to 1.0 μg/mL. The ED_{50} was less than 0.13 μg/mL at ACV concentrations above 2.0 μg/mL. 100% protection was observed with 0.13 μg/mL zidovudine plus 8 μg/mL ACV. The sum of fractional inhibitory concentrations is 0.14, indicating synergism. No potentiation of bone marrow cytotoxicity was observed.

Resistance

The development of resistance to zidovudine has been studied extensively. The emergence of resistance is a function of both duration of zidovudine therapy and stage of disease. Asymptomatic patients developed resistance at significantly slower rates than patients with advanced disease. In contrast, virus isolates from patients with AIDS who received a year or more of zidovudine may show more than 100-fold increases in ID_{50} compared to isolates pre-therapy.

In vitro resistance to zidovudine is due to the accumulation of specific mutations in the HIV reverse transcriptase coding region. Six amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg, Leu210Trp, Thr215→Tyr or Phe, and Lys219→Gln) have been described in viruses with decreased *in vitro* susceptibility to zidovudine inhibition. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by the accumulation of at least four to six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for the subsequent use of other approved reverse transcriptase inhibitors.

A significant correlation between zidovudine resistance and poor clinical outcome in children with advanced disease has been reported; in addition, a correlation between reduced sensitivity to zidovudine and lower CD4 cell counts in symptom-free adults treated with zidovudine for up to three years has also been reported. However, the specific relationship between emergence of zidovudine resistance and clinical progression of disease in adults has not yet been defined.

Cross-Resistance

The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. *In vitro* studies with zidovudine-resistant virus isolates indicate zidovudine-resistant strains are usually sensitive to zalcitabine and didanosine. Combination therapy with zidoduvine plus 3TC® delayed the emergence of mutations conferring resistance to zidovudine. In some patients (4/34) harboring zidovudine-resistant virus, combination therapy with zidoduvine plus 3TC® restored phenotypic sensitivity to zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for $\geq$1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different ($Ala^{62}\rightarrow Val$, $Val^{75}\rightarrow Ile$, $Phe^{77}\rightarrow Leu$, $Phe^{116}\rightarrow Tyr$ and $Gln^{151}\rightarrow Met$) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine. A second pattern, typically involving a Thr69Ser mutation plus a 6 base-pair inserted at the same position, results in a phenotypic resistance to zidovudine as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

Other Retroviruses

Zidovudine has antiviral activity against some other mammalian retroviruses in addition to HIV. Human immunodeficiency Virus-2 (HIV-2) replication *in vitro* is inhibited by zidovudine with an ID_{50} of 0.015 µg/mL, while HTLV-1 transmission to susceptible cells is inhibited by 1 to 3 µg/mL concentrations of drug. Several strains of simian immunodeficiency virus (SIV) are also inhibited by zidovudine with ID_{50} values ranging from 0.13 to 6.5 µg/mL, depending upon species of origin and assay method used.

Non-Retroviruses

Zidovudine has been tested and found to be inactive *in vitro* as an inhibitor of Herpes Simplex Virus type 1, Adenovirus type 5, Coronavirus, Influenza A virus, Respiratory Syncytial virus, Measles virus, Rhinovirus IB, Bovine Rotavirus and Yellow Fever virus. Zidovudine had significant inhibitory activity against the Epstein-Barr virus with an ID_{50} of 1.4 to 2.7 μg/mL, but the clinical significance of this is unknown.

Other Microbiological Activities

The following microbiological activities of zidovudine have been observed *in vitro* but the clinical significance is unknown. Many Enterobacteriaceae, including strains of *Shigella*, *Salmonella*, *Klebsiella*, *Enterobacter*, *Citrobacter* and *Escherichia coli* are inhibited *in vitro* by low concentrations of zidovudine (0.005 to 0.5 μg/mL). Synergy of zidovudine with trimethoprim has been observed against some of these bacteria *in vitro*. Limited data suggest that bacterial resistance to zidovudine develops rapidly. Zidovudine has no activity against gram-positive organisms, anaerobes, mycobacteria, or fungal pathogens including *Candida albicans* and *Cryptococcus neoformans*. Although *Giardia lamblia* is inhibited by 1.9 μg/mL of zidovudine, no activity was observed against other protozoal pathogens.

***In Vivo* Antiviral Activity**

The antiviral efficacy of zidovudine was assessed in BALB/c mice infected with Rauscher murine leukemia virus. Treatment with 15 mg/kg/day led to significant prolongation of life. No deaths occurred within 24 weeks in infected zidovudine-treated mice, whereas control animals given the same inoculum had a median survival of 36 days ($p<0.001$). Bone marrow depression did not occur, but these doses of zidovudine did not prevent significant splenomegaly. At a dose of 145 mg/kg/day, drug toxicity was observed (3 of the 4 mice developed >20% weight loss, severe white and red cell depression, and corneal opacities) although a significant survival advantage was shown for zidovudine-treated animals compared to control infected mice (p=0.03). These mice also had no evidence of viral replication after treatment and splenomegaly did not develop.

Efficacy of zidovudine therapy was assessed in healthy cats infected with feline leukemia virus. Eight of the 10 treated cats had some reduction in the number of FeLV antigen positive white blood cells and bone marrow cells.

PHARMACOLOGY

Pharmacokinetics

Adults

The pharmacokinetics of zidovudine has been evaluated in 22 adult HIV-infected patients in a Phase I dose-escalation study. Cohorts of 3 to 7 patients received 1 hour intravenous infusions of zidovudine ranging from 1 to 2.5 mg/kg every 8 hours to 2.5 to 7.5 mg/kg every 4 hours (3 to 45 mg/kg/day) for 14 to 28 days followed by oral dosing ranging from 2 to 5 mg/kg every 8 hours to 5 to 10 mg/kg every 4 hours (6 to 60 mg/kg/day) for an additional 32 days. After oral dosing, zidovudine was rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours. Dose-independent kinetics were observed over the range of 2 mg/kg every 8 hours to 10 mg/kg every 4 hours. The mean zidovudine half-life was approximately 1 hour and ranged from 0.78 to 1.93 hours following oral dosing.

Total body clearance averaged 1900 mL/min/70 kg and the apparent volume of distribution was 1.6 L/kg. Renal clearance is estimated to be 400 mL/min/70 kg indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine plasma protein binding is 34 to 38%, indicating that drug interactions involving binding site displacement are not anticipated.

The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio was determined in 39 patients receiving chronic therapy with zidoduvine. The median ratio measured in 50 paired samples drawn 1 to 8 hours after the last dose of zidoduvine was 0.6.

Zidovudine is rapidly metabolized to 3'-azido-3'-deoxy-5'-*0*-β-*D*- glucopyranuronosyl thymidine (GZDV) which has an apparent elimination half-life of 1 hour (range 0.61 to 1.73 hours). Following oral administration, urinary recovery of zidovudine and GZDV accounted for 14% and 74% of the dose, respectively, and the total urinary recovery averaged 90% (range 63% to 95%), indicating a high degree of absorption. However, as a result of first-pass metabolism, the average oral capsule bioavailability of zidovudine is 65% (range 52% to 75%). A second metabolite, 3'-amino-3'-deoxythymidine (AMT) has been identified in the plasma following single dose intravenous administration of zidovudine. AMT area-under-the-curve (AUC) was one-fifth of the AUC of zidovudine and had a half-life of 2.7±0.7 hours. In comparison, GZDV AUC was about 3-fold greater than the AUC of zidovudine.

Capsules

Steady-state serum concentrations of zidovudine following chronic oral administration of 250 mg every 4 hours were determined in 21 adult patients in a controlled trial. Mean steady-state predose and 1.5 hours post-dose zidovudine concentrations were 0.16 µg/mL (range 0 to 0.84 µg/mL) and 0.62 µg/mL (range 0.05 to 1.46 µg/mL), respectively.

Adults with Impaired Renal Function

The pharmacokinetics of zidovudine has been evaluated in patients with impaired renal function following a single 200 mg oral dose. In 14 patients (mean creatinine clearance 18±2 mL/min), the half-life of zidovudine was 1.4 hours compared to 1.0 hour for control subjects with normal renal function; AUC values were approximately twice those of controls. Additionally, GZDV half-life in these patients was 8.0 hours (vs 0.9 hours for control) and AUC was 17 times higher than for control subjects. The pharmacokinetics and tolerance were evaluated in a multiple-dose study in patients undergoing hemodialysis (n=5) or peritoneal dialysis (n=6). Patients received escalating doses of zidovudine up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well-tolerated despite significantly elevated plasma levels of GZDV. Total body clearance after oral administration of zidovudine was approximately 50% of that reported in patients with normal renal function. The plasma concentrations of AMT are not known in patients with renal insufficiency. Daily doses of 300 to 400 mg should be appropriate in HIV-infected patients with severe renal dysfunction. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, whereas GZDV elimination is enhanced.

Syrup

In a multiple-dose bioavailability study conducted in 12 HIV-infected adults receiving doses of 100 or 200 mg every four hours, zidovudine syrup was demonstrated to be bioequivalent to zidovudine capsules with respect to area under the zidovudine plasma concentration time curve (AUC). The rate of absorption of zidovudine syrup was greater than that of zidovudine capsules, as indicated by mean times to peak concentration of 0.5 and 0.8 hours, respectively. Mean values for steady-state peak concentration (dose-normalized to 200 mg) were 1.5 and 1.2 μg/mL for syrup and capsules, respectively.

<u>Effect of Food on Absorption</u>

Administration of zidoduvine capsules with food decreased peak plasma concentrations by greater than 50%. However, bioavailability as determined by AUC may not be affected.

<u>Children and Infants</u>

The mean oral bioavailability of 65% was independent of dose. This value is the same as the bioavailability in adults. Doses of 180 mg/m^2 four times daily in pediatric patients produced similar systemic exposure (24 hour AUC 10.7 hr•µg/mL) as doses of 200 mg six times daily in adult patients (10.9 hr•µg/mL).

The pharmacokinetics of zidovudine has been studied in neonates from birth to 3 months of life. In one study of the pharmacokinetics of zidovudine in women during the last trimester of pregnancy, zidovudine elimination was determined immediately after birth in 8 infants who were exposed to zidovudine *in utero*. The half-life was 13.0±5.8 hours. In another study, the pharmacokinetics of zidovudine was evaluated in infants (ranging in age of 1 day to 3 months) of normal birth weight for gestational age and with normal renal and hepatic function. In infants less than or equal to 14 days old, mean±SD total body clearance was 10.9±4.8 mL/min/kg (n=18) and half-life was 3.1±1.2 hours (n=21). In infants greater than 14 days, total body clearance was 19.0±4.0 mL/min/kg (n=16) and half-life was 1.9±0.7 hours (n=18). Bioavailability was 89%±19% (n=15) in the younger age group and decreased to 61%±19% (n=17) in infants older than 14 days.

Concentrations of zidovudine in cerebrospinal fluid were measured after intermittent oral administration in 21 children during Phase I and Phase II studies. The mean zidovudine CSF/plasma concentration ratio measured at an average time of 2.2 hours post-dose at doses of 120 to 240 mg/m^2 was 0.52±0.44 (n=28).

As in adult patients, the major route of elimination in children was by metabolism to GZDV. Overall, the pharmacokinetics of zidovudine in pediatric patients older than 3 months of age is similar to that of zidovudine in adult patients.

Pregnancy

The pharmacokinetics of zidovudine has been studied in a Phase 1 study of eight women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in five pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see PRECAUTIONS).

TOXICOLOGY

Acute Toxicity Studies

Acute toxicity studies in mice and rats at doses up to 750 mg/kg produced only one death, in a mouse given 487 mg/kg of zidovudine. Death was preceded by chronic convulsions. Decreased activity, ptosis and laboured breathing were noted in other animals for up to 35 minutes post-dose. No effects were seen during the 14-day post-dose observation period.

In a second set of acute toxicity studies at higher doses, the median lethal doses for mice were 3568 mg/kg and 3062 mg/kg for male and female, respectively. In rats, the median lethal doses were 3084 mg/kg for males and 3683 mg/kg for females.

Clinical signs noted prior to death included ptosis, decreased activity, ataxia, body tremors, urine stains and prostration in mice. In rats, decreased activity and salivation occurred in most animals; the males receiving 5000 mg/kg also exhibited rough coats and lacrimation.

Long-Term Toxicity Studies

Oral

Rats and monkeys received zidovudine by gavage, dogs were administered the capsules.

Species	No. per Group M	No. per Group F	Dose Levels (mg/kg/day)	Duration weeks	Effects
CD Rat	5	5	0, 60,125, 250, 500	2	Post-dose salivation. Weight loss in mid-dose (1/5) and high-dose (1/5) males.
CD Rat	12	12	0, 56, 167, 500	13	Anogenital staining in high-dose rats. Increased blood glucose levels in high-dose females at term. Occasional decreases in SGOT in both sexes at high dose.
CD Rat	25	25	0, 50, 150, 450	52	Salivation at high dose for the first 4 weeks. Moderate, reversible macrocytic anemia, with reticulocytosis, in the high-dose animals. Increased urine output in some high-dose animals.
Dog	1	1	0, 125, 250, 500	2	High-dose female sacrificed day 14, following 2 days emesis. High-dose male had bloody vomitus on days 11, 14, 16. Marked leukopenia and thrombocytopenia in all treated dogs, most severe in high-dose. Alk. phos., BUN and creatinine increased in high-dose female. Slight increase in kidney weight in both high-dose dogs and in mid-dose male. Focal to diffuse hemorrhage in Gl tract and mesentery of both high-dose dogs and mid-dose female. Moderate hypoactivity in the lymph nodes, involution of the thymus (mid- and high-dose females, high-dose male) and splenic lymphoid atrophy (high-dose male only). Dose-related mild to marked hypocellularity of the bone marrow at all dose levels.

Monkey (Cynomolgus)	1	1	0, 125, 250, 500	2	Emesis in high-dose male. Decreased RBC, hematocrit and hemoglobin in all groups (all values within normal range). Increased SGPT in mid- and high-dose males, more marked in high-dose females.
Monkey (Cynomolgus)	4	4	0, 34, 100, 300	13	Emesis in one high-dose male. Mild to moderate decrease in RBC, HCT and HB; slight to mild increase in MCV in mid- and high-dose groups. Slight decrease in WBC in high-dose males.
Monkey (Cynomolgus	5	5	0, 35, 100, 300	26	Decreased RBC, HCT and HB in all groups, generally dose-related. Increase in MCV and MCH more prominent in males. Dose-related retardation of bone marrow cell maturation, particularly in erythroid elements. Slight, inconsistent, increase in platelets in mid- and high-dose group.
Monkey (Cynomolgus)	6	6	Males-35, 100, 300 Females-35, 100, 300	52	Dose-related macrocytic anemia (i.e., decreased RBC, HCT and HB, increased MCV and MCH) maximized by week 26 at latest. After 4 weeks recovery, the bone marrow smears were similar in control and treated animals. The severity of anemia was similar to that in the 3-month and 6-month study.

Carcinogenesis

Zidovudine was administered orally at three 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 300 mg/kg/day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (5 non-metastasizing squamous cell carcinomas, one squamous cell papilloma and one 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, two late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumors occurred at the low or middle doses in rats.

No other drug-related tumors were observed in either sex of either species.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg per day or 40 mg/kg per day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately three 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 (~1000 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.

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

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.

Mutagenesis

No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames *Salmonella* mutagenicity assay at concentrations up to 10 μg per plate, which was the maximum concentration that could be tested because of the antimicrobial activity of zidovudine against the *Salmonella* species. In a mutagenicity assay conducted in L5178Y/TK+/- mouse lymphoma cells, zidovudine was weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4000 and 5000 μg/mL). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1000 μg/mL and higher. In an *in vitro* mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 μg/mL and higher. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 μg/mL and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1.0 μg/mL. In an *in vivo* cytogenetic study in rats given a single intravenous injection of zidovudine at doses of 37.5 to 300 mg/kg, there were no treatment-related structural or numerical chromosomal alterations in spite of plasma levels that were as high as 453 μg/mL five minutes after dosing.

In two *in vivo* micronucleus studies (designed to measure chromosome breakage or mitotic spindle apparatus damage) in male mice, oral doses of zidovudine of 100 to 1000 mg/kg/day administered once daily for approximately 4 weeks induced dose-related increases in micronucleated erythrocytes. Similar results were also seen after 4 or 7 days of dosing at 500 mg/kg/day in rats and mice.

In a study involving 11 AIDS patients, it was reported that the seven patients who were receiving zidoduvine (1200 mg/day) as their only medication for 4 weeks to 7 months showed a chromosome breakage frequency of 8.29±2.65 breaks per 100 peripheral lymphocytes. This was significantly ($p<0.05$) higher than the incidence of 0.5±0.29 breaks per 100 cells that was observed in the four AIDS patients who had not received zidoduvine. A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. The clinical significance of these findings is unknown.

Reproduction and Teratology

In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation.

No effect on male or female fertility (judged by conception rates) was seen in rats given zidovudine orally at doses up to 450 mg/kg/day.

In a fertility and reproduction study, male rats were dosed for 85 days prior to mating and females for 26 days prior to mating and throughout gestation and lactation. No fetal malformations or variations occurred, but the mid- and high-doses were both embryotoxic, increasing the number of early resorptions and decreasing litter sizes. No embryotoxic effects occurred in untreated females mated with treated males.

No evidence of teratogenicity was found in rats given oral doses of zidovudine of up to

500 mg/kg/day on days 6 through 15 of gestation. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats of 66 to 226 times the peak human plasma concentrations.

In a second teratology study in rats, an oral dose of 3000 mg/kg/day (very near the oral median lethal dose in rats of 3683 mg/kg/day) caused marked maternal toxicity and an increase in the incidence of fetal malformations including absent tail, anal atresia, fetal edema, situs inversus, diaphragmatic hernia, bent limb bones, atlas occipital defect and vertebral and/or rib anomalies. There was also a significant increase in the number of litters with bent ribs, reduced ossification of the vertebral arches, and presacral vertebrae. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated area-under-the-curve 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 the experiment at doses of 600 mg/kg/day or less.

In one of two studies in pregnant rabbits, the incidence of fetal resorptions was increased in rabbits given 500 mg/kg/day. There was no evidence of a teratogenic effect at any dose level. The doses used in these studies resulted in peak zidovudine plasma concentrations in rabbits of 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).

Peri- and Post-natal Studies

A separate peri- and post-natal study was conducted in pregnant rats given doses of 0, 50, 150 and 400 mg/kg/day from day 17 of gestation through to day 21 of lactation. There were no adverse effects noted in either generation. The reproductive capacity of those F1 generation pups which were raised to sexual maturity was not affected.

Neonatal animals were given 0, 80, 250 or 750 mg/kg/day for two months, starting on lactation day 8. Treatment-related alterations occurred only in the high-dose group and were reversible macrocytic anemia and increased urine output in both sexes, and decreased body weight gain in males. Mild to moderate increases in spleen weights were also noted.

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