PRODUCT MONOGRAPH

PrAPO-ZIDOVUDINE

Zidovudine Capsules USP

100 mg

Antiretroviral Agent

APOTEX INC.
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Control# 233343

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Zidovudine Capsules USP
100 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Capsules/100 mg	colloidal silicon dioxide, microcrystalline cellulose, starch and stearic acid. The capsule, imprinted with edible black ink, contains gelatin and titanium dioxide.

INDICATIONS AND CLINICAL USE

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

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 initiating combination therapy with zidovudine.

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

CONTRAINDICATIONS

- APO-ZIDOVUDINE (zidovudine) is contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulations (see DOSAGE FORMS, COMPOSITION AND PACKAGING section).

- Due to the active ingredient zidovudine, APO-ZIDOVUDINE is contraindicated in patients with abnormally low neutrophil counts (< 0.75 x 10^9/L) or abnormally low hemoglobin levels (< 7.5 g/dL or 4.65 mmol/L).

WARNINGS AND PRECAUTIONS

Anemia (usually not observed before six weeks of zidovudine therapy but occasionally occurring earlier), neutropenia (usually not observed before four weeks therapy but sometimes occurring earlier) and leucopenia (usually secondary to neutropenia) can be expected to occur in patients with advanced symptomatic HIV disease receiving zidovudine. These occurred more frequently at higher dosages (1200 to 1500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease.

Hematological parameters should be carefully monitored. For patients with advanced symptomatic HIV disease it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter.

Dosage reduction or interruption of zidovudine therapy may be necessary in patients whose hemoglobin level falls to between 7.5 g/dL (4.65 mmol/L) and 9 g/dL (5.59 mmol/L) or whose neutrophil count falls to between 0.75 x 10^9/L and 1.0 x 10^9/L

General

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.

Before combination therapy with APO-ZIDOVUDINE is initiated, consult the complete prescribing information for each drug. The safety profile of APO-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.

Endocrine and Metabolism

Lipoatrophy
Treatment with zidovudine has been associated with loss of subcutaneous fat. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs and buttocks, may be only partially reversible and improvement may take several months when switching to a zidovudine-free regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine and other zidovudine containing products (COMBIVIR and TRIZIVIR), and if feasible, therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

Serum lipids and blood glucose
Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations

should be managed as clinically appropriate.

Hematologic

Bone Marrow Suppression

APO-ZIDOVUDINE (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 section). There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuation of the drug.

Hepatic/Biliary/Pancreatic

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Rare occurrences of lactic acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis, (even in the absence of marked transaminase elevations) have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, 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 zidovudine develops unexplained tachypnea, dyspnea, or a fall in serum bicarbonate level. Under these circumstances, therapy with zidovudine should be suspended until the diagnosis of lactic acidosis has been excluded.

Clinical features which may be indicative of the development of lactic acidosis include generalized weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnea and tachypnea).

Caution should be exercised when administering zidovudine to any patient, particularly to those with known risk factors for liver disease (obese women, hepatomegaly, hepatitis, or other known risk factors). These patients should be followed closely while on therapy with zidovudine. 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 zidovudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

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

Data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Dosage adjustments may be necessary, but as there is only limited data available precise recommendations cannot be made. If monitoring of plasma zidovudine levels is not feasible, physicians will need to monitor for signs of intolerance and adjust the dose and/or increase the interval between doses as appropriate.

Patients co-infected with hepatitis C virus:
Exacerbation of anemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. Therefore, the co-administration of ribavirin and zidovudine is not advised and consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This is particularly important in patients with a known history of zidovudine induced anemia.

Use With Interferon- and Ribavirin- Based Regimens:
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/HCV virologic suppression) was seen when ribavirin was coadministered with zidovudine in HIV/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and APO-ZIDOVUDINE should be closely monitored for treatment-associated toxicities, especially hepatic decompensation, neutropenia, and anemia. Discontinuation of APO-ZIDOVUDINE should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g. Child Pugh >6) (see the complete prescribing information for interferon and ribavirin).

Immune

Immune Reconstitution Inflammatory Syndrome

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

Autoimmune disorders (such as Graves' disease, polymyositis, autoimmune hepatitis and Guillain-Barre 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 and sometimes can be an atypical presentation.

Musculoskeletal

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

Renal

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 sections). 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.

Hemodialysis and peritoneal dialysis have no significant effect on zidovudine elimination whereas elimination of the glucuronide metabolite is increased. For patients with end-stage renal disease maintained on hemodialysis or peritoneal dialysis, the recommended dose is 100 mg every 6 to 8 h (see Pharmacokinetics).

Special Populations

Pregnancy, Fertility and Reproduction:
The safe use of APO-ZIDOVUDINE in human pregnancy has not been established in adequate and well-controlled trials investigating congenital abnormalities. Therefore administration of APO-ZIDOVUDINE in pregnancy should be considered only if the expected benefit outweighs the possible risk to the fetus.

There are no data on the effect of zidovudine on human female fertility. In men, zidovudine has been shown to have no effect on sperm count, morphology, or motility.

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.

APO-ZIDOVUDINE has been associated with findings in animal reproductive studies (see TOXICOLOGY section). Pregnant women considering using APO-ZIDOVUDINE during pregnancy should be made aware of these findings.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peripartum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peripartum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to ART (antiretroviral therapy), including zidovudine, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients:

http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

APO-ZIDOVUDINE has been evaluated in the Antiretroviral Pregnancy Registry in over 13,000 women during pregnancy and postpartum. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for APO-ZIDOVUDINE compared to the background rate.

The Antiretroviral Pregnancy Registry has received reports of over 13,000 exposures to APO-ZIDOVUDINE during pregnancy resulting in live birth. These consist of over 4,100 exposures during the first trimester, over 9,300 exposures during the second/third trimester and included 133 and 264 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.7, 3.8%) and in the second/third trimester, 2.8% (2.5, 3.2%). This proportion is not significantly higher than those reported in the two population based surveillance systems (2.72 per 100 live births and 4.17 per 100 live births respectively). The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for APO-ZIDOVUDINE compared to the background rate.

Nursing Women:
HIV-1 infected mothers should not breastfeed their infants to avoid risking postnatal transmission of HIV. Zidovudine is excreted in human milk at similar concentrations to those found in serum. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving APO-ZIDOVUDINE.**

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.

Geriatrics:

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. However, since special care is advised in this age group due to age-associated changes such as the decrease in renal function and alterations in hematological parameters, appropriate monitoring of patients before and during use of zidovudine is advised.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults

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 zidovudine. 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 section).

The following Table 1 summarizes the relative incidence of hematologic adverse events observed in clinical studies by severity of HIV disease present at the start of treatment:

Table 1 Relative Incidence of Hematologic Adverse Events Observed in Clinical Studies By Severity of HIV Disease Present at the Start of Treatment.

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 <7.5 g/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	51% (n=262)	37% (n=262)	39% (n=262)	29% (n=262)

* 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 2 summarizes clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1500mg/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 2 Percentage (%) of Patients with Clinical Events in Advanced HIV Disease 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	2
NERVOUS		
Dizziness	6	4
Insomnia	5	1
Paresthesia	6	3
Somnolence	8	9
RESPIRATORY		
Dyspnea	5	3
SKIN		
Rash	17	15
SPECIAL SENSES		
Taste Perversion	5	8

* 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 in patients treated with zidovudine, their possible relationship to the drug is unknown.

Body as a whole: Back pain, body odour, chest pain, chills, edema of the lip, flu syndrome, hyperalgesia, lymphadenopathy

Cardiovascular: Vasodilation

Gastrointestinal: Bleeding gums, constipation, dysphagia, edema of the tongue, eructation, flatulence, mouth ulcer, rectal hemorrhage

Musculoskeletal: Arthralgia, muscle spasm, tremor, twitch

Nervous: Anxiety, confusion, depression, emotional lability, loss of mental acuity, nervousness, syncope, vertigo

Respiratory: Cough, epistaxis, hoarseness, pharyngitis, rhinitis, sinusitis

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 Table 3 and Table 4 summarize all those events reported significantly more frequently by patients receiving zidovudine in these studies:

Table 3 Percentage (%) of Patients with Clinical Events in 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 4 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 AND PRECAUTIONS section).

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 5 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 5 Number and Percentage (%) of Patients with Clinical Adverse Experiences Occurring in >3% of Patients Considered Possibly or Probably Related to Study Drug

'HIVD' + Zidovudine Combination Trial Pooled Concomitant Regimens	**N3447/ACTG 106 * No Prior Zidovudine**			
	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)

* Median duration of treatment ranged from 22 weeks 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 6 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 6 The Occurrence of Anemia (Hgb < 7.5 g/dL) and Granulocytopenia (< 750 cells/mm3) Among 124 Children Receiving Zidovudine for a Mean of 267 days

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

* Twenty-two children received one or more transfusions due to a decline in hemoglobin to <7.5 g/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 7:

Table 7 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

Combination Therapy with Zidovudine and Lamivudine

Pediatric Patients

Selected clinical adverse events and physical findings with a ≥ 5% frequency during therapy with lamivudine 4 mg/kg twice daily plus zidovudine 160 mg/m2 three times daily compared with didanosine in patients without, or with, minimal (≤ 56 days) prior antiretroviral therapy are listed in Table 8.

Table 8 Selected Clinical Adverse Events and Physical Findings (≥ 5% Frequency) in Pediatric Patients in Study ACTG300

Adverse Event	Lamivudine plus Zidovudine (n = 236)	Didanosine (n = 235)
Body as a whole		
Fever	25%	32%
Digestive		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%

Respiratory		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
Ear, Nose and Throat		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
Other		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

*Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by patients without or minimal (≤ 56 days) prior antiretroviral therapy are listed in Table 9.

Table 9 Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study ACTG300

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

ULN = Upper limit of normal.
ANC = Absolute neutrophil count.

Post-Market Adverse Drug Reactions

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.

Hematological: Anemia (which may require transfusions), neutropenia, leucopenia, aplastic anemia, thrombocytopenia, pancytopenia (with marrow hypoplasia) and pure red cell aplasia. Anemia, neutropenia, leucopenia and aplastic anemia occur more frequently at higher dosages (1200-1500 mg/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 section). 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.

Body as a Whole:	Loss of subcutaneous fat (see WARNINGS AND PRECAUTIONS section: **Endocrine and Metabolism, Lipoatrophy**). Convulsions, cardiomyopathy (thrombocytopenia, pancytopenia).
Gastrointestinal*:*	Oral mucosa pigmentation.
Immune System:	Immune Reconstitution Inflammatory Syndrome (see WARNINGS AND PRECAUTIONS: Immune section)
Liver/pancreas:	Raised blood levels of liver enzymes and bilirubin.
Metabolism & Nutrition disorders:	Anorexia, hyperlactatemia, lactic acidosis (see WARNINGS AND PRECAUTIONS section: Hepatic/Biliary/Pancreatic, Lactic Acidosis/Severe Hepatomegaly with Steatosis).
Miscellaneous:	Gynecomastia. Myopathy, hyperlactatemia.
Skin:	Sweating. Nail and skin discoloration.

DRUG INTERACTIONS

Overview

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated.

Drug-Drug Interactions

Table 10 Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Atovaquone	Zidovudine does not appear to affect the pharmacokinetics of atovaquone.	Pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a three week, concomitant course of atovaquone for the treatment of acute PCP would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.
Bone marrow suppressive agents/cytotoxic agents	Coadministration may increase risk of hematologic toxicity.	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.
Clarithromycin	Clarithromycin tablets reduce the absorption of zidovudine.	This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.
Fluconazole	Fluconazole interferes with the oral clearance and metabolism of zidovudine	Preliminary data suggests 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.
Ganciclovir	Coadministration increases the risk of hematologic toxicities in some patients with advanced HIV disease.	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 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.

Proper name	Effect	Clinical comment
Lamivudine	Coadministration resulted in an increase in C_{max} of zidovudine.	Zidovudine and lamivudine were coadministered to 12 asymptomatic HIV- positive patients in a single-centre, 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 C_{max} of zidovudine.
Methadone	Plasma levels of zidovudine can be elevated in some patients while remaining unchanged in others.	In a pharmacokinetic study of 9 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.
Phenytoin	A decrease in oral zidovudine clearance.	Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. These observations suggest that phenytoin levels should be carefully monitored in patients receiving both medicinal products. 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.
Probenecid	May increase zidovudine levels.	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.
Ribavarin	Coadministration of ribavirin and zidovudine may lead to increased ribavirin levels and increased risk of anemia.	Preliminary data suggest that the use of ribavirin and zidovudine lead to increased ribavirin levels and increased risk of anemia. The use of ribavirin concomitantly with zidovudine in the treatment of HIV / Hep C co-infected patients is not advised. Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established.

Proper name	Effect	Clinical comment
Stavudine	Zidovudine may inhibit intracellular phosphorylation of stavudine	Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Stavudine is therefore not recommended to be used in combination with zidovudine.
Valproic acid	Increase in zidovudine AUC and a decrease in the plasma GZDV AUC.	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 6 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.
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. Other active substances including but not limited to acetylsalicylic acid, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of interactions before using such medicinal products, particularly for chronic therapy, in combination with zidovudine. Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (for example systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. If concomitant therapy with any of these medicinal products is necessary then extra care should be taken in monitoring renal function and hematological parameters and, if required, the dosage of one or more agents should be adjusted.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

DOSAGE AND ADMINISTRATION

Dosing Considerations

Monitoring of Patients
Hematologic toxicities appear to be related to pre-treatment 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 section). 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.

Recommended Dose and Dosage Adjustment

Oral Administration

Adults and Adolescents 30 kg and Over
The recommended total oral daily dose 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 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 11.

Table 11 Suggested Dosing Regimens for Adults and Adolescents (30 kg and Over)

Formulation	Dosing Regimen	
Capsules	**Twice daily (every 12 hours)**	**Three times daily (every 8 hours)**
	Three 100 mg Capsules	**Two 100 mg Capsules**

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 section). 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 renal disease patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours (see **Pharmacokinetics** section of DETAILED PHARMACOLOGY).

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

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 non-specific 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.

Activated charcoal should be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

Patients should be observed closely for evidence of toxicity (see Adverse Reactions) and given the necessary supportive therapy.

Hemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

For management of a suspected drug overdose, please contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Pharmacokinetics
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.

STORAGE AND STABILITY

APO-ZIDOVUDINE Capsules should be stored between 15°C to 25°C and protected from light and moisture.

SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-ZIDOVUDINE Capsules 100 mg (white, opaque body with white, opaque cap) are imprinted "APO Z100" and contain 100 mg of zidovudine.
Available in bottles of 100, 500 and 1000, and in unit dose packages of 100.

Composition
Each capsule contains 100 mg zidovudine and the non-medicinal ingredients colloidal silicon dioxide, microcrystalline cellulose, starch and stearic acid. The capsule, imprinted with edible black ink, contains gelatin and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

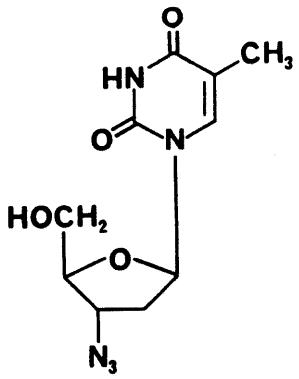
Proper name: Zidovudine

Chemical name: 3'-azido-3'deoxythymidine

Other names: erythro-3'-azidothymidine, BW A509U, 509U81, azidothymidine (AZT)

Molecular formula and molecular mass: $C_{10}H_{13}N_5O_4$ 267.24 g/mol

Structural formula:



Zidovudine

Physicochemical properties:

Description: zidovudine is a white to beige, odourless, crystalline solid. It has a melting point of 122°C to 124°C and solubility in water of 20 mg/mL at 25°C.

CLINICAL TRIALS

Comparative Bioavailability

A single dose, 2-way crossover relative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 31 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of zidovudine was measured and compared following a single oral dose (1 x 100 mg capsule) of Apo-Zidovudine (zidovudine) 100 mg capsule (Apotex Inc.) and Retrovir® (zidovudine) 100 mg capsule (Burroughs Wellcome (Canada)).

Zidovudine (1 x 100 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUCT (ng•h/mL)	528 544 (24)	528 542 (22)	100	94.2 - 106
AUCI (ng•h/mL)	550 565 (23)	550 563 (21)	100.0	94.2 – 106.0
Cmax (ng/mL)	433 478 (44)	403 430 (37)	106.9	89.5 – 127.6
Tmax§ (h)	0.70 (0.46)	0.70 (0.29)		
T½ § (h)	1.02 (0.15)	1.02 (0.16)		

* Apo–Zidovudine (zidovudine) 100 mg capsules (Apotex Inc.)

† Retrovir® (zidovudine) 100 mg capsules (Burroughs Wellcome (Canada)) were purchased in Canada.

§ Expressed as arithmetic means (standard deviation) only.

DETAILED PHARMACOLOGY

Pharmacokinetics

Adults

The zidovudine cerebrospinal fluid (CSF)/plasma concentration ratio was determined in 39 patients receiving chronic therapy with zidovudine. The median ratio measured in 50 paired samples drawn 1 to 8 hours after the last dose of zidovudine 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 mcg/mL (range 0 to 0.84 mcg/mL) and 0.62 mcg/mL (range 0.05 to 1.46 mcg/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.

Hepatic Impairment
Data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Dosage adjustments may be necessary, but as there is only limited data available precise recommendations cannot be made (see DOSAGE AND ADMINISTRATION).

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

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 neonatal 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 WARNINGS AND PRECAUTIONS section).

MICROBIOLOGY

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 (-OH) group is replaced by an azido (-N3) 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 (α-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 ≤ 0.13 mcg/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 mcg/mL (ID_{50}) in both HIV-infected H9 cells and peripheral blood lymphocytes. Zidovudine at concentrations of 0.13 mcg /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 mcg/mL in one laboratory to 13.3 mcg/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 mcg /mL and ID_{95} sensitivity values between 0.03 to 0.3 mcg/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 mcg/mL. However, one human T-lymphocyte cell line was sensitive to the cytotoxic effect of zidovudine with an ID_{50} of 5 mcg/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 mcg/mL was estimated. Two of 10 human lymphocyte cultures tested were found to be sensitive to zidovudine at 5 mcg/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 mcg/mL. The ED_{50} decreased to 0.40 mcg/mL in the presence of 0.5 mcg/mL ACV and was further decreased to 0.22 mcg/mL when the ACV concentration was increased to 1.0 mcg/mL. The ED_{50} was less than 0.13 mcg/mL at ACV concentrations above 2.0 mcg/mL. 100% protection was observed with 0.13 mcg/mL zidovudine plus 8 mcg/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, Leu210→Trp, 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 zidovudine plus lamivudine delayed the emergence of mutations conferring resistance to zidovudine. In some patients (4/34) harbouring zidovudine-resistant virus, combination therapy with zidovudine plus lamivudine 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 ≥ 1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr and Gln151→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 mcg/mL, while HTLV-1 transmission to susceptible cells is inhibited by 1 to 3 mcg/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 mcg/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 ID50 of 1.4 to 2.7 mcg/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 mcg/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 mcg/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.

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

The results of long-term toxicity studies in rats, dogs and monkeys are presented in Table 14 below**.** Rats and monkeys received zidovudine by gavage, dogs were administered zidovudine capsules.

Table 14 Long – Term Toxicity Studies with Zidovudine in Rats, Dogs and Monkeys

Species	**No. per Group**		**Dose Levels (mg/kg/day)**	**Duration (weeks)**	**Effects**
	M	F			
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 emesis. High-dose male had bloody vomitus on days 11, 14, 16. Marked leucopenia 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 GI 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 tumours 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 tumours occurred at the low or middle doses in rats.

No other drug-related tumours 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 tumours was noted with no increase in tumours 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 tumours 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 rodent carcinogenicity studies may be for humans. At doses that produced tumours 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 mcg 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 mcg/mL). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1000 mcg/mL and higher. In an *in vitro* mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 mcg/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 mcg/mL and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1.0 mcg/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 mcg /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 zidovudine (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 zidovudine. 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 Postnatal Studies

A separate peri- and postnatal 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.

REFERENCES

1. Alvarez D, Dieterich DT, Brau N, Moorehead L, Ball L, Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. J Viral Hepat 2006 Oct;13(10):683-9.

2. Arenas-Pinto A, Grant AD, Edwards S, Weller IV. Lactic acidosis in HIV infected patients: a systematic review of published cases. Sex Transm Infect 2003; 79(4):340-344.

3. Barret B, Tardieu M, Rustin P, Lacroix C, Chabrol B, Desguerre I, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. AIDS 2003; 17(12):1769-1785.

4. Boubaker K, Flepp M, Sudre P, Furrer T, Haensel A, Hirschel B, et al. Hyperlactatemia and Antiretroviral therapy: The Swiss HIV Cohort Study. HIV/AIDS CID 2000; 33: 1931-7.

5. Carr A. HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management. AIDS 2003; 17 Suppl 1:S141-S148.

6. Carr A. Lactic acidemia in infection with human immunodeficiency virus. Clin Infect Dis 2003; 36(Suppl 2):S96-S100.

7. Creagh-Kirk T, Doi P, Andrews E, Nusinoff-Lehrman S, Tilson H, Hoth D, et al. Survival experience among patients with AIDS receiving zidovudine. Follow-up of patients in a compassionate plea program. JAMA 1988; 260(2):3009-3015.

8. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1- infected persons after initiation of highly active antiretroviral therapy. Ann Intern Med 2000; 133(6):447-454.

9. Easterbrook PJ, Keruly JC, Creagh-Kirk T, Richman DD, Chaisson RE, Moore RD. Racial and ethnic differences in outcome in zidovudine-treated patients with advanced HIV disease. Zidovudine Epidemiology Study Group. JAMA 1991; 266: 2713-2718.

10. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 1987; 317(4): 185-91.

11. Fischl MA, Richman DD, Causey DM, Grieco MH, Bryson Y, Mildvan D, et al. Prolonged zidovudine therapy in patients with AIDS and advanced AIDS-related complex. AZT Collaborative Working Group. JAMA 1989; 262(17): 2405-2410.

12. Harrigan P.R., Kemp SD, Kinghorn I, Bloor S, Kohli A, St.Clair BA, et al. A placebo controlled trial of AZT alone or in combination with DDI or DDC: Viral Load and Drug Resistance: Abstracts of 2nd International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland. AIDS 1994; Vol. 8 (suppl 4).

13. Hirsch H, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV- infected patients. Clin Infect Dis 2004; 38(8):1159-1166.

14. Iversen AK, Shafer RW, Wehrly K, Winters MA, Mullins JI, Chesebro B, et al. Multidrug-resistant human immunodeficiency virus type 1 strains resulting from combination antiretroviral therapy. J Virol 1996; 70(2):1086-1090.

15. Johnson VA, Quinn JB, Benoit SL, Wagner SF, Overbay CB, Wagner JR, et al. Drug Resistance and Viral Load In NUCA3002: Lamivudine (#TC) (High or Low Dose)/Zidovudine (ZDV) combination Therapy in ZDV-Experienced (≥24 weeks) patients (CD4 cells 100-300/mm^3). Abstracts of the 3rd Conference on Retroviruses and Opportunistic Infections, Washington DC. Abs No 321.

16. Lagakos S, Fischl MA, Stein DS, Lim L, Volberding P. Effects of zidovudine therapy in minority and other subpopulations with early HIV infection. JAMA 1991; 266 (19): 2709-2712.

17. Lee BL, Tauber MG, Sadler B, Goldstein D, Chambers HF. Atovaquone inhibits the glucuronidation and increases the plasma concentrations of zidovudine. Clin Pharmacol Ther 1996; 59(1): 14-21.

18. Lertora JJ, Rege AB, Greenspan DL, Akula S, George WJ, Hyslop NE, Jr., et al. Pharmacokinetic interaction between zidovudine and valproic acid in patients infected with human immunodeficiency virus. Clin Pharmacol Ther 1994; 56 (3): 272-278.

19. Lonergan JT, Havlir D, Barber E, Mathews WC, et al. Incidence of symptomatic hyperlactatemia in HIV-infected adults on NRTI's 9th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, USA, 24 Feb-28 Feb 2002: 2002; 35.

20. McKinney RE, Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naïve HIV-1 infection. J Pediatrics 1998; 133(4):400-508.

21. Meng TC, Fischl MA, Boota AM, Spector SA, Bennett D, Bassiakos Y, et al. Combination Therapy with zidovudine and dideoxycytidine in patients with advanced human immunodeficiency virus infection. Ann Intern Med 1992; 116(1):13-20.

22. Mihovilovic M, Richman DP. Monoclonal antibodies as probes of the alpha- bungarotoxin and cholinergic binding regions of the acetylcholine receptor. J Biol Chem 1987; 262(11):4978-4986.

23. Mirmirani P, Maurer TA, Herndier B, McGrath M, Weinstein MD, Berger TG. Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome. J Am Acad Dermatol 1999; 41(2 Pt 2):285-286.

24. Moyle GJ, Datta D, Mandalia S, Morlese J, Asboe D, Gazzard BG. Hyperlactataemia and lactic acidosis during antiretroviral therapy: relevance, reproducibility and possible risk factors. AIDS 2002; 16(10):1341-1349.

25. Olivero OA, Shearer GM, Chougnet CA, Kovacs AA, Landay AL, Baker R, et al. Incorporation of zidovudine into leukocyte DNA from HIV-1-positive adults and pregnant women, and cord blood from infants exposed *in utero*. AIDS 1999; 13(8): 919-925.

26. Perronne C. Antiviral hepatitis and antiretroviral drug interactions. J Hepatol 2006;44(1 Suppl):S119-S125.

27. Pizzo PA, Eddy J, Falloon J, Balis FM, Murphy RF, Moss H, et al. Effect of continuous infusion of zidovudine (AZT) in children with symptomatic HIV infection. N Engl J Med 1988; 319(14):889-896.

28. Ramos A, Asensio A, Perales I, Montero MC, Martin T. Prolonged paradoxical reaction of tuberculosis in an HIV-infected patient with initiation of highly active antiretroviral therapy. Eur J Clin Microbiol Infect Dis 2003; 22(6):374-376.

29. Rendon AL, Nunez M, Romero M, Barreiro P, Martin-Carbonero L, Garcia- Samaniego J, et al. Early monitoring of ribavirin plasma concentrations may predict anemia and early virologic response in HIV/hepatitis C virus-coinfected patients. J Acquir Immune Defic Syndr 2005 Aug 1; 39(4):401-5.

30. Richman DD, Fischl MA, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 1987; 317(4): 192-7.

31. Rodriguez-Torres M, Torriani FJ, Soriano V, Borucki MJ, Lissen E, Sulkowski M, et al. Effect of ribavirin on intracellular and plasma pharmacokinetics of nucleoside reverse transcriptase inhibitors in patients with human immunodeficiency virus-hepatitis C virus coinfection: results of a randomized clinical study. Antimicrob Agents Chemother 2005 Oct; 49(10):3997-4008.

32. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL, et al. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. Clin Infect Dis 2002; 35(10):1250-1257.

33. Salama C, Policar M, Venkataraman M. Isolated pulmonary Mycobacterium avium complex infection in patients with human immunodeficiency virus infection: case reports and literature review. Clin Infect Dis 2003; 37(3):e35-e40.

34. Schmitt FA, Bigley JW, McKinnis R, Logue PE, Evans RW, Drucker JL.Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex. N Engl J Med 1988; 319(24): 1573-1578.

35. Shelburne SA, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL, Musher DM, et al. Immune Reconstitution Inflammatory Syndrome. Medicine 2002; 81(3): 213-227.

36. Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. AIDS 2007 May 31; 21(9):1073-89.

37. Shepp DH, Ramirez-Ronda C, Dall L, Pollard RB, Murphy RL, Kessler M, et al. A comparative trial of zidovudine administered every four versus every twelve hours for the treatment of advanced HIV disease. Acquir Immune Defic Syndr Hum Retrovirol 1997; 15(4):283-288.

38. Thaker H, Ong LC. Localized Mycobacterium avium complex infection in a patient on HAART. Clin Microbiol Infect 2000; 6(10):564-566.

39. Trevenzoli M, Cattelan AM, Marino F, Marchioro U, Cadrobbi P. Sarcoidosis and HIV infection: a case report and a review of the literature. Postgrad Med J 2003; 79(935):535-538.

40. Volberding PA, Lagakos SW, Koch MA, Pettinelli C, Myers MW, Booth DK, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. N Engl J Med 1990; 322(17): 941-949.

41. Product Monograph –RETROVIR® (AZT) Zidovudine Capsules USP, 100 mg Zidovudine Syrup, 50 mg/5mL Zidovudine for Injection, 10 mg/mL ViiV Healthcare ULC. Date of Revision: July 4, 2019 (Submission Control No: 226223).

PART III: CONSUMER INFORMATION

[Pr]APO-ZIDOVUDINE
Zidovudine Capsules 100mg USP

This leaflet is part III of a three-part "Product Monograph" published when APO-ZIDOVUDINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-ZIDOVUDINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
The name of your medicine is APO-ZIDOVUDINE.
APO-ZIDOVUDINE can only be obtained with a prescription from your doctor. APO-ZIDOVUDINE is an antiretroviral medication. It is used together with other antiviral medicines to delay the progression of HIV infection.

APO-ZIDOVUDINE is prescribed to slow down the effects of HIV virus; it is not a cure.

What it does:
The Human Immunodeficiency Virus (HIV) is a retrovirus.
Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

APO-ZIDOVUDINE is an antiretroviral medication. It is used together with other antiviral medicines to delay the progression of HIV infection. APO-ZIDOVUDINE does not cure AIDS or kill the HIV virus, but helps to prevent further damage to the immune system by slowing down the production of new viruses.

When it should not be used:

APO-ZIDOVUDINE should not be used in patients:
- who have potentially life-threatening allergic reactions to any component of the formulations (see what the important nonmedicinal ingredients are).
- with low blood cell counts (anemia) or low hemoglobin levels (blood component which carries oxygen in the blood).

What the medicinal ingredient is:
APO-ZIDOVUDINE contains zidovudine.

What the important nonmedicinal ingredients are:
Each capsule contains the non-medicinal ingredients colloidal silicon dioxide, microcrystalline cellulose, starch and stearic acid . The capsule, imprinted with edible black ink, contains gelatin and titanium dioxide.

What dosage forms it comes in:
APO-ZIDOVUDINE is available as zidovudine capsules USP (100 mg/capsule)

WARNINGS AND PRECAUTIONS

BEFORE you use APO-ZIDOVUDINE talk to your doctor or pharmacist if:
- you are allergic to any ingredient in this medicine.
- you have bone marrow problems (low blood cell counts).
- you have hepatomegaly (enlarged liver), hepatitis (inflamed liver) or other known risk factors for liver disease.
- you have kidney disease.
- you are taking other drugs (see Interactions with this medication).
- you are pregnant or breastfeeding.
- your baby or infant was exposed to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) during pregnancy or labour.
- you are taking ribavarin as it could cause or worsen anemia (symptoms of tiredness, shortness of breath). Your doctor will advise whether you should stop taking APO-ZIDOVUDINE.

Illness 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.

Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

Use of This Medication During Pregnancy and Breast Feeding
Before you use APO-ZIDOVUDINE, talk to your doctor or pharmacist if you are pregnant, planning to become pregnant, or become pregnant while taking APO-ZIDOVUDINE. It is not known if APO-ZIDOVUDINE can harm your unborn child. You and your doctor will need to decide if taking APO-ZIDOVUDINE is right for you. If you take APO-ZIDOVUDINE while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.

Babies and infants exposed to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) during pregnancy or labour, show minor temporary increases in blood levels of lactate. The clinical importance of these temporary increases is unknown.

There have been very rare reports of diseases that affect the nervous system such as delayed development and seizures.

These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies.

HIV-infected women should not breastfeed in order to prevent transmission of HIV to a child who may not yet be infected. The ingredients in APO-ZIDOVUDINE can also pass into your breast-milk.

INTERACTIONS WITH THIS MEDICATION

Some drugs may change the usefulness and safety of APO-ZIDOVUDINE. It is therefore very important that you tell your doctor before you decide to take any new drugs, even if these are available without a prescription.

Drugs that may interact with APO-ZIDOVUDINE include: atovaquone, bone marrow suppressive agents/cytotoxic agents, clarithromycin, fluconazole, ganciclovir, interferon-alpha, lamivudine, methadone, phenytoin, probenecid, stavudine, valproic acid, and others such as trimethoprim- sulfamethoxazole, pyrimethamine, acyclovir and rifampin.

For patients receiving combination therapy with APO-ZIDOVUDINE 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, 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 APO-ZIDOVUDINE are presently unknown. If you are a female of child-bearing age, you should use effective contraception while using zalcitabine.

An additional precaution is that some other drugs may change the usefulness and safety of APO-ZIDOVUDINE.

PROPER USE OF THIS MEDICATION

Usual dose:
You should be counselled about the use of APO-ZIDOVUDINE.
It is important to take APO-ZIDOVUDINE exactly as prescribed. Altering the dose without the direct advice of your physician is unwise, as is sharing your medication with others.

Oral Administration
Adults and Adolescents 30 kg and Over
The recommended total oral daily dose of APO-ZIDOVUDINE is 600 mg per day in divided doses in combination with other antiretroviral agents. Suggested Dosing Regimens:

- three 100 mg APO-ZIDOVUDINE capsules every 12 hours; OR two 100 mg APO-ZIDOVUDINE capsules every 8 hours.

If you are also taking clarithromycin, your doctor may advise you to take this medication at least 2 hours before or 2 hours after APO-ZIDOVUDINE, to avoid a drug interaction.

Overdose:

If you think you have taken too much APO-ZIDOVUDINE, contact your healthcare professional,, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFETS AND WHAT TO DO ABOUT

THEM

Side-effects of APO-ZIDOVUDINE include nausea, vomiting, fever, headache, stomach pain, loss of appetite, muscle pain, low white blood cell count (neutropenia or leucopenia), decrease in the number of cells involved in blood clotting (thrombocytopenia) or in all kinds of blood cells (pancytopenia), reduction in the number of red blood cells (pure red cell aplasia), failure of the bone marrow to produce new blood cells (aplastic anemia), an increase in lactic acid, feeling depressed or anxious, dizziness, not being able to sleep, tingly feelings in the skin (pins and needles), not being able to concentrate, feeling drowsy, seizures, disease of the heart muscle, cough, intestinal gas, changes in the colour of the nails, skin, or the skin inside the mouth, taste disturbance, indigestion, skin rash (red, raised or itchy skin), sweating, passing urine more often, enlarged breasts in men, general aches and pain, chills, chest pain, flu-like feeling. If these become bothersome, consult your doctor.

Treatment with APO-ZIDOVUDINE or other medicines that contain zidovudine may cause a loss of fat from legs, arms and face (lipoatrophy). Your doctor should monitor for signs of lipoatrophy. Tell your doctor if you notice any loss of fat from your legs, arms, and face. When these signs occur, your doctor will assess if APO-ZIDOVUDINE should be stopped and your HIV treatment changed. If you stop taking APO-ZIDOVUDINE it may take several months to see any lost fat return. You may not regain all of your lost body fat.

Changes to your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

Autoimmune disorders (when the immune system attacks healthy body tissue), may also occur after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver).

Autoimmune disorders may occur many months after the start of treatment. Look for any other symptoms such as:

- high temperature (fever), redness, rash, swelling
- fatigue
- joint or muscle pain
- numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations (chest pain) or rapid heart rate

If you notice these or any symptoms of inflammation or infection, tell your doctor immediately.

Serious side effects and what to do about them

Frequency	Side Effect/ Symptoms (2 or more of the following)	Talk to your healthcare professional		Stop taking drug and and get immediate medical help
		Only if severe	In all cases	
Common	Lowered red blood cell count (anemia) – resulting in fatigue, breathlessness. Low white blood cell count (neutropenia) - making you more prone to infections.			✓
Rare	Pancreatitis (inflammation of the pancreas) and symptoms such as nausea, vomiting, and severe stomach cramps.			✓
	Lactic acidosis (high level of acid in the blood) and symptoms such as weight loss, fatigue, malaise, abdominal pain, shortness of breath.			✓
Rare	Severe hepatomegaly (swollen and enlarged liver) with symptoms of liver problems such as nausea, vomiting, abdominal pain, weakness and diarrhea.			√

An important but reversible side-effect of zidovudine, particularly in patients with more severe disease, can be a decrease in certain types of blood counts (including red blood cells, white blood cells and platelets) and increase in certain liver enzymes. 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 advanced disease and in patients who start zidovudine therapy late in their illness.

Contact your doctor if you experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis (which include very severe stomach cramps) or any other unexpected adverse events while being treated with APO-ZIDOVUDINE.

This is not a complete list of side effects. For any unexpected effects while taking APO-ZIDOVUDINE, contact your doctor or pharmacist.

HOW TO STORE IT

APO-ZIDOVUDINE Capsules should be stored at room temperature between 15ºC to 25ºC and protected from light and moisture.

As with all medicines, keep APO-ZIDOVUDINE out of reach and sight of children.

Do not take your medicine after the expiry date shown on the bottle and the carton.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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

If you want more information about APO-ZIDOVUDINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

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