1. NAME OF THE MEDICINAL PRODUCT

Zidovudine Tablets USP 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Label claim

Each film coated tablet contains

Zidovudine USP 300mg

List of Excipients:

Microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, film coat {Hypromellose, Titanium dioxide, Polyethylene glycol 400}

3. PHARMACEUTICAL FORM

Immediate release, film coated tablets (solid oral dosage form)

Description

White to off – white, round, biconvex tablet, debossed with "M106" on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC indications

Zidovudine Tablets is indicated as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.

4.2 Posology and method of administration

Adults: The recommended oral dose of Zidovudine is 600 mg per day in divided doses in combination with other antiretroviral agents.

Pediatrics: The recommended dose in pediatric patients 6 weeks to 12 years of age is 160 mg/m^2 every 8 hours (480 mg/m^2/day up to a maximum of 200 mg every 8 hours) in combination with other antiretroviral agents.

Maternal-Fetal HIV Transmission: The recommended dosing regimen for administration to pregnant women (>14 weeks of pregnancy) and their neonate is:

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

Neonatal Dosing: 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered Zidovudine intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours.

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

Dose Adjustment: ***Anemia:*** Significant anemia (hemoglobin of <7.5 g/dL or reduction of >25% of baseline) and/or significant neutropenia (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. In patients who develop significant anemia, dose interruption does not necessarily eliminate the need for transfusion. If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoetin level and patient tolerance.

For patients experiencing pronounced anemia while receiving chronic co-administration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) zidovudine dose reduction may be considered.

End-Stage Renal Disease: In patients maintained on hemodialysis or peritoneal dialysis, recommended dosing is 100 mg every 6 to 8 hours.

Hepatic Impairment: There are insufficient data to recommend dose adjustment of Zidovudine in patients with mild to moderate impaired hepatic function or liver cirrhosis. Since Zidovudine is primarily eliminated by hepatic metabolism, a reduction in the daily dose may be necessary in these patients.

4.3 Contraindications

Zidovudine Tablets, Capsules, and Syrup are contraindicated for patients who have potentially life-threatening allergic reactions to any of the components of the formulations.

4.4 Special warning and precautions for use

COMBIVIR and TRIZIVIR are combination product tablets that contain zidovudine as one of their components. Zidovudine tablet should not be administered concomitantly with COMBIVIR or TRIZIVIR.

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

Bone Marrow Suppression: Zidovudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1,000 cells/mm^3 or hemoglobin <9.5 g/dL. In patients with advanced symptomatic HIV disease, anemia and neutropenia were the most significant adverse events observed. There have been reports of pancytopenia associated with the use of Zidovudine, which was reversible in most instances after discontinuance of the drug. However, significant anemia, in many cases requiring dose adjustment, discontinuation of Zidovudine, and/or blood transfusions, has occurred during treatment with Zidovudine alone or in combination with other antiretrovirals.

Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with Zidovudine. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anemia or neutropenia develops, dosage adjustments may be necessary.

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

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

Precautions

General: Zidovudine is eliminated from the body primarily by renal excretion following metabolism in the liver (glucuronidation). In patients with severely impaired renal function (CrCl<15 mL/min), dosage reduction is recommended. Although the data are limited, zidovudine concentrations appear to be increased in patients with severely impaired hepatic function which may increase the risk of hematologic toxicity.

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

Fat Redistribution: Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast

enlargement, and "cushingoid appearance," have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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

The safety and efficacy of Zidovudine in women, intravenous drug users, and racial minorities is not significantly different than that observed in white males.

Patients should be informed that the major toxicities of Zidovudine are neutropenia and/or anemia. The frequency and severity of these toxicities are greater in patients with more advanced disease and in those who initiate therapy later in the course of their infection. They should be told that if toxicity develops, they may require transfusions or drug discontinuation. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced symptomatic HIV disease. They should be cautioned about the use of other medications, including ganciclovir and interferon alfa, which may exacerbate the toxicity of Zidovudine. Patients should be informed that other adverse effects of Zidovudine include nausea and vomiting. Patients should also be encouraged to contact their physician if they experience muscle weakness, shortness of breath, symptoms of hepatitis or pancreatitis, or any other unexpected adverse events while being treated with Zidovudine.

Zidovudine Tablets are for oral ingestion only. Patients should be told of the importance of taking Zidovudine exactly as prescribed. They should be told not to share medication and not to exceed the recommended dose. Patients should be told that the long-term effects of Zidovudine are unknown at this time.

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, including the possible risk of cancer. HIV-infected pregnant women should be advised not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected. Patients should be advised that therapy with Zidovudine has not been shown to reduce the risk of transmission of HIV to others Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

Use with Interferon- and Ribavirin-Based Regimens: Hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa and ribavirin. Patients receiving interferon alfa with or without ribavirin and zidovudine should be closely monitored for treatment-associated toxicities, especially neutropenia, anemia, and hepatic decompensation. Discontinuation of zidovudine should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening of clinical toxicities are observed, including hepatic decompensation (e.g., Childs Pugh >6). No evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was co-administered with zidovudine. However, HIV/HCV co-infected patients who were administered zidovudine in combination with pegylated interferon and ribavirin developed severe neutropenia (ANC <500) and severe anemia (hemoglobin <8 g/dL) more frequently than similar patients not receiving zidovudine (neutropenia 15% vs. 9%, anemia 5% vs. 1%).

Overlapping Toxicities: Co administration of ganciclovir, interferon alfa, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

4.6 Pregnancy and lactation

Pregnancy: Pregnancy Category C. Oral teratology studies in the rat and in the rabbit at doses up to 500 mg/kg/day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg/day and rabbits given 500 mg/kg/day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an in vitro experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation. In an additional teratology study in rats, a dose of 3,000 mg/kg/day (very near the

oral median lethal dose in rats of 3,683 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. (Estimated area under the curve [AUC] in rats at this dose level was 300 times the daily AUC in humans given 600 mg/day.) No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg/day or less.

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Zidovudine is excreted in human milk. 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 zidovudine.

4.8 Undesirable effects

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

Percentage (%) of Patients with Adverse Events* in Asymptomatic HIV Infection

Adverse Event	Zidovudine 500 mg/day (n = 453)	Placebo (n = 428)
Body as a whole		
Asthenia	8.6%†	5.8%
Headache	62.5%	52.6%
Malaise	53.2%	44.9%
Gastrointestinal		
Anorexia	20.1%	10.5%
Constipation	6.4%†	3.5%
Nausea	51.4%	29.9%
Vomiting	17.2%	9.8%

* Reported in ≥5% of study population.

† Not statistically significant versus placebo.

In addition to the adverse events listed above, other adverse events observed in clinical studies were abdominal cramps, abdominal pain, arthralgia, chills, dyspepsia, fatigue,

hyperbilirubinemia, insomnia, musculoskeletal pain, myalgia, and neuropathy. Selected laboratory abnormalities observed during a clinical study of monotherapy with Zidovidone are:

Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Patients with Asymptomatic HIV Infection

Adverse Event	Zidovudine 500 mg/day (n = 453)	Placebo (n = 428)
Anemia (Hgb<8 g/dL)	1.1%	0.2%
Granulocytopenia (<750 cells/mm^3)	1.8%	1.6%
Thrombocytopenia (platelets<50,000/mm^3)	0%	0.5%
ALT (>5 x ULN)	3.1%	2.6%
AST (>5 x ULN)	0.9%	1.6%
Alkaline phosphatase (>5 x ULN)	0%	0%

ULN = Upper limit of normal.

Pediatrics: Selected clinical adverse events and physical findings with a ≥5% frequency during therapy with Lamivudine 4 mg/kg twice daily plus Zidovidone 160 mg/m^2 3 times daily compared with didanosine in therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are:

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

Adverse Event	Lamivudine plus Zidovidone (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 therapy-naive (≤56 days of antiretroviral therapy) pediatric patients are:
Frequencies of Selected (Grade 3/4) Laboratory Abnormalities in Pediatric Patients

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

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

Additional adverse events reported in open-label studies in pediatric patients receiving Zidovudine 180 mg/m^2 every 6 hours were congestive heart failure, decreased reflexes, ECG abnormality, edema, hematuria, left ventricular dilation, macrocytosis, nervousness/irritability, and weight loss.
The clinical adverse events reported among adult recipients of Zidovudine may also occur in pediatric patients.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Mode of action:
Zidovudine is an antiviral agent which is highly active *in vitro* against retroviruses including the Human Immunodeficiency Virus (HIV).
Zidovudine is phosphorylated in both infected and uninfected cells to the monophosphate (MP) derivative by cellular thymidine kinase. Subsequent phosphorylation of zidovudine-MP to the diphosphate (DP), and then the triphosphate (TP) derivative is catalysed by cellular thymidylate kinase and non-specific kinases respectively. Zidovudine-TP acts as an inhibitor of and substrate

for the viral reverse transcriptase. The formation of further proviral DNA is blocked by incorporation of zidovudine-MP into the chain and subsequent chain termination. Competition by zidovudine-TP for HIV reverse transcriptase is approximately 100-fold greater than for cellular DNA polymerase alpha.

Clinical virology:
The relationships between *in vitro* susceptibility of HIV to zidovudine and clinical response to therapy remain under investigation. *In vitro* sensitivity testing has not been standardised and results may therefore vary according to methodological factors. Reduced *in vitro* sensitivity to zidovudine has been reported for HIV isolates from patients who have received prolonged courses of zidovudine therapy. The available information indicates that for early HIV disease, the frequency and degree of reduction of *in vitro* sensitivity is notably less than for advanced disease.

The reduction of sensitivity with the emergence of zidovudine resistant strains limits the usefulness of zidovudine monotherapy clinically. In clinical studies, clinical end-point data indicate that zidovudine, particularly in combination with lamivudine, and also with didanosine or zalcitabine results in a significant reduction in the risk of disease progression and mortality. The use of a protease inhibitor in a combination of zidovudine and lamivudine, has been shown to confer additional benefit in delaying disease progression, and improving survival compared to the double combination on its own.

The anti-viral effectiveness *in vitro* of combinations of anti-retroviral agents are being investigated. Clinical and *in vitro* studies of zidovudine in combination with lamivudine indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Furthermore there is clinical evidence that zidovudine plus lamivudine delays the emergence of zidovudine resistance in anti-retroviral naive patients.

In some *in vitro* studies zidovudine has been shown to act additively or synergistically with a number of anti-HIV agents, such as lamivudine, didanosine, and interferon-alpha, inhibiting the replication of HIV in cell culture. However, *in vitro* studies with triple combinations of nucleoside analogues or two nucleoside analogues and a protease inhibitor have been shown to be more effective in inhibiting HIV-1 induced cytopathic effects than one or two drug combinations.

Resistance to thymidine analogues (of which zidovudine is one) is well characterised and is conferred by the stepwise accumulation of up to six specific mutations in the HIV reverse transcriptase at codons 41, 67, 70, 210, 215 and 219. 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 of the 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 any of the other approved reverse transcriptase inhibitors.

Two patterns of multi-drug resistance mutations, the first characterised by mutations in the HIV reverse transcriptase at codons 62, 75, 77, 116 and 151 and the second involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to AZT 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.

In a clinical trial, zidovudine was shown to be effective in reducing the rate of maternal-foetal transmission of HIV-1 (23% infection rate for placebo versus 8% for zidovudine) when administered (100 mg five times daily) to HIV-positive pregnant women (from week 14-34 of pregnancy) and their newborn infants (2 mg/kg every 6 hours) until 6 weeks of age. In the shorter duration 1998 Thailand CDC study, use of oral zidovudine therapy only (300 mg twice daily), from week 36 of pregnancy until delivery, also reduced the rate of maternal-foetal transmission of HIV (19% infection rate for placebo versus 9% for zidovudine). These data, and data from a published study comparing zidovudine regimes to prevent maternal-foetal HIV transmission have shown that short maternal treatments (from week 36 of pregnancy) are less efficacious than longer maternal treatments (from week 14-34 of pregnancy) in the reduction of perinatal HIV transmission.

5.2 Pharmacokinetic properties

Pharmacokinetics:
Adults: Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hours. Binding to plasma protein is low. Zidovudine is primarily eliminated by hepatic metabolism. The major metabolite of zidovudine is 3'-azido-3'-deoxy-5'-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74%, respectively, of the dose following oral administration. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (IV) administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC. Pharmacokinetics of zidovudine was dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

The extent of absorption (AUC) was equivalent when zidovudine was administered as zidovudine Tablets or Syrup compared to zidovudine Capsules.

Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients

Parameter	Mean ± SD (except where noted)
Oral bioavailability (%)	64 ± 10 (n = 5)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 8)
Plasma protein binding (%)	<38
CSF:plasma ratio*	0.6 [0.04 to 2.62] (n = 39)

Systemic clearance (L/hr/kg)	1.6 ± 0.6 (n = 6)
Renal clearance (L/hr/kg)	0.34 ± 0.05 (n = 9)
Elimination half-life (hr)[†]	0.5 to 3 (n = 19)

[*] Median [range].

[†] Approximate range.

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

Zidovudine Pharmacokinetic Parameters in Patients with Severe Renal Impairment[*]

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

[*] Data are expressed as mean ± standard deviation.

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

Adults with Impaired Hepatic Function: Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic.

Pediatrics:

Patients from 3 Months to 12 Years of Age: Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral

solution from 90 to 240 mg/m^2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV.

Patients Younger Than 3 Months of Age: Zidovudine pharmacokinetics have been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In neonates ≤14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients >14 days old.

Zidovudine Pharmacokinetic Parameters in Pediatric Patients*

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

* Data presented as mean ± standard deviation except where noted.

† Median [range].

Pregnancy: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to those of non pregnant 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 5 pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

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

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

Effect of Food on Absorption: Zidovudine may be administered with or without food. The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food.

5.3 Preclinical safety data

Mutagenicity:

No evidence of mutagenicity was observed in the Ames test. However, zidovudine was weakly mutagenic in a mouse lymphoma cell assay and was positive in an *in vitro* cell transformation assay. Clastogenic effects were observed in an *in vitro* study in human lymphocytes and in *in vivo* oral repeat dose micronucleus studies in rats and mice. An *in vivo* cytogenetic study in rats did not show chromosomal damage. A study of the peripheral blood lymphocytes of eleven AIDS patients showed a higher chromosome breakage frequency in those who had received zidovudine than in those who had not. 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. A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

Carcinogenicity:

In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. A subsequent intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours were the result of long term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other drug-related tumours observed in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. One study, by the US National Cancer Institute, administered zidovudine at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation. One year post-natally, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment related findings were limited to late-occurring vaginal epithelial tumours, which were seen with a similar incidence

and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

It is concluded that the transplacental carcinogenicity data from the first study represents a hypothetical risk, whereas the reduction in risk of maternal transfection of HIV to the uninfected child by the use of zidovudine in pregnancy has been well proven.

5. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate, film coat {Hypromellose, Titanium dioxide, Polyethylene glycol 400}

6.3 Shelf life
60 months

6.4 Special precautions for storage
Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

Pack
HDPE bottle of 60's.

References

1. SmPC of Retrovir Capsules {Glaxo SmithKline, UK}
2. Prescribing information of Retrovir Tablets {Glaxo SmithKline, USA}
3. Physician Desk Reference 60th edition {Pg. No. 1533 - 1537}

7. APPLICANT/MANUFACTURER

Marketing Authorization Holder

HEALTHLINE LIMITED

Manufactured by

Mylan Laboratories Limited
F-4 & F-12, MIDC, Malegaon,
Sinnar, Nashik - 422 113,
Maharashtra, INDIA