# RETROVIR

**Zidovudine**

## QUALITATIVE AND QUANTITATIVE COMPOSITION

*RETROVIR* 100 mg Capsules

Hard gelatin capsules with opaque white cap and body and a central dark-blue band, printed "Wellcome", "100" and coded Y9C and each containing 100 mg Zidovudine.

*RETROVIR* 250 mg Capsules

Hard gelatin capsules with opaque blue cap, opaque white body and a central dark-blue band, printed "Wellcome", "250" and coded H2F and each containing 250 mg Zidovudine.

*RETROVIR* Oral Solution

Oral solution containing 50 mg zidovudine per 5 ml. It is clear, pale yellow, and strawberry-flavoured. Contains sodium benzoate.

## PHARMACEUTICAL FORM

Hard capsules.

Oral solution.

## CLINICAL PARTICULARS

### Indications

*RETROVIR* is indicated in combination with other anti-retroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children.

### Dosage and Administration

*RETROVIR* therapy should be initiated by a physician experienced in the management of HIV infection.

- **Dosage in adults and adolescents weighing at least 30 kg**

The recommended dose of *RETROVIR* in combination with other anti-retroviral agents is 250 or 300 mg twice daily.

- **Dosage in children**

*Children weighing at least 9 kg and less than 30 kg:*

The recommended dose of *RETROVIR* is 0.9mL/kg (9 mg/kg) twice daily in combination with other anti-retroviral agents (e.g. a 15 kg child would require a 13.5 mL dose of oral solution twice daily). The maximum dosage should not exceed 300 mg (30mL) twice daily.

*Children weighing at least 4 kg and less than 9 kg:*

The recommended dose of *RETROVIR* is 1.2mL/kg (12 mg/kg) twice daily in combination with other antiretroviral agents (e.g. a 5 kg neonate would require a 6 mL dose of oral solution twice daily).

Available data are insufficient to propose specific dosage recommendations for children weighing less than 4 kg (*see below – Pregnancy and Lactation and Pharmacokinetics*).

- **Elderly**

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 haematological parameters, appropriate monitoring of patients before and during use of *RETROVIR* is advised.

- **Renal impairment**

In patients with severe renal impairment daily dosages of 300 to 400 mg should be appropriate. Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. Haemodialysis and peritoneal dialysis have no significant effect on *RETROVIR* elimination whereas elimination of the glucuronide metabolite is increased. For patients with end-stage renal disease maintained on haemodialysis or peritoneal dialysis, the recommended dose is 100 mg every 6 to 8 hours (*see Pharmacokinetics*).

- **Hepatic impairment**

Limited 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 precise recommendations cannot be made at present. If monitoring of plasma zidovudine levels is not feasible, physicians will need to pay particular attention to signs of intolerance and increase the interval between doses as appropriate.

- **Dosage adjustments in patients with haematological adverse reactions**

Dosage adjustments may be necessary in patients with haematological adverse reactions. This is more likely in patients with poor bone marrow reserve prior to treatment, particularly in patients with advanced HIV disease. If the haemoglobin level falls to between 7.5g/dl (4.65mmol/l) and 9g/dl (5.59mmol/l) or the neutrophil count falls to between 0.75 x $10^9$/l and 1.0 x $10^9$/l, the daily dosage may be reduced until there is evidence of marrow recovery; alternatively, recovery may be enhanced by a brief (2-4 weeks) interruption of *RETROVIR* therapy. If dosage reduction is considered, the daily dosage may, for example, be halved and subsequently increased, depending on patient tolerance, up to the original dosage. Therapy with *RETROVIR* should be interrupted if the haemoglobin level falls below 7.5g/dl (4.65mmol/l) or the neutrophil count falls to less than 0.75 x $10^9$/l (*see Contraindications, Warnings and Precautions*). Marrow recovery is usually

observed within 2 weeks after which time *RETROVIR* therapy at a reduced dosage may be reinstituted. After a further 2-4 weeks the dosage may be gradually increased, depending on patient tolerance, up to the original dosage.

## Contraindications

*RETROVIR* is contraindicated in patients known to be hypersensitive to zidovudine, or to any of the component of the formulations.

*RETROVIR* should not be given to patients with abnormally low neutrophil counts (less than 0.75 x $10^9$/l) or abnormally low haemoglobin levels (less than 7.5g/dl or 4.65mmol/l) (*see Warnings and Precautions*).

## Warnings and Precautions

Patients should be cautioned about the concomitant use of self-administered medications (*see Interactions*).

Patients should be advised that *RETROVIR* therapy has not been proven to prevent the transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

*RETROVIR* is not a cure for HIV infection and patients remain at risk of developing illnesses which are associated with immune suppression, including opportunistic infections and neoplasms. Whilst it has been shown to reduce the risks of opportunistic infections, data on the development of neoplasms, including lymphomas, are limited. The available data on patients treated for advanced HIV disease indicates that the risk of lymphoma development is consistent with that observed in untreated patients. In patients with early HIV disease on long-term treatment the risk of lymphoma development is unknown.

Pregnant women considering the use of *RETROVIR* during pregnancy for prevention of HIV transmission to their infants should be advised that transmission may still occur in some cases despite therapy.

***Haematological adverse reactions****:* Anaemia (usually not observed before 6 weeks of *RETROVIR* therapy but occasionally occurring earlier), neutropenia (usually not observed before 4 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 *RETROVIR*. These occurred more frequently at higher dosages (1200-1500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease.

Haematological parameters should be carefully monitored. For patients with advanced symptomatic HIV disease it is generally recommended that blood tests are performed at least every 2 weeks for the first 3 months of therapy and at least monthly thereafter. In patients with early HIV infection (where bone marrow reserve is generally good), haematological adverse reactions are less infrequent. Depending on the overall condition of the patient, blood tests may be performed less often, for example every 1-3 months.

If the haemoglobin level falls to between 7.5 g/dl (4.65 mmol/l) and 9 g/dl (5.59 mmol/l) or the neutrophil count falls to between 0.75 x $10^9$/l and 1.0 x $10^9$/l, the daily dosage may be reduced until there is evidence of marrow recovery; alternatively, recovery may be enhanced by brief (2-4 weeks) interruption of *RETROVIR* therapy. Marrow recovery is usually observed within 2 weeks after which time *RETROVIR* therapy at a reduced dosage may be reinstituted. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (*see Contraindications*).

***Lactic acidosis/severe hepatomegaly with steatosis****:* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including zidovudine. A majority of these cases have been women.

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 (dyspnoea and tachypnoea).

Caution should be exercised when administering *RETROVIR*, particularly to those with known risk factor for liver disease. Treatment with *RETROVIR* 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).

***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 *RETROVIR* 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 should be managed as clinically appropriate.

***Immune Reconstitution Syndrome (IRIS):*** In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* (*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis 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.

***Patients co-infected with hepatitis C virus:*** Exacerbation of anaemia 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 anaemia.

## Interactions

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. Active substances which are primarily eliminated by hepatic metabolism especially via glucuronidation may have the potential to inhibit metabolism of zidovudine. The interactions listed below should not be considered exhaustive but are representative of the classes of drug where caution should be exercised.

**Atovaquone**: Zidovudine does not appear to affect the pharmacokinetics of atovaquone. However, 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.

**Clarithromycin**: Clarithromycin tablets reduce the absorption of zidovudine. This can be avoiding by separating the administration of zidovudine and clarithromycin by at least two hours.

**Lamivudine**: A modest increase in $C_{max}$ (28%) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

**Phenytoin**: Phenytoin blood levels have been reported to be low in some patients receiving *RETROVIR*, while in one patient a high level was noted. These observations suggest that phenytoin levels should be carefully monitored in patients receiving both drugs.

**Probenecid**: Limited data suggest that probenecid increases the mean half-life and AUC of zidovudine by decreasing glucuronidation. Renal excretion of the glucuronide (and possibly zidovudine itself) is reduced in the presence of probenecid.

**Rifampicin**: Limited data suggests that co-administration of zidovudine and rifampicin decreases AUC of zidovudine by 48% $\pm$ 34%. However the clinical significance of this is unknown.

**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 *RETROVIR*.

**Miscellaneous**: Other drugs including but not limited to aspirin, 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 drug interactions before using such drugs, particularly for chronic therapy, in combination with *RETROVIR*.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive drugs (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to *RETROVIR*. If concomitant therapy with any of these drugs is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.

Exacerbation of anaemia 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 anaemia.

Since some patients receiving *RETROVIR* may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such prophylaxis has included co-trimoxazole, aerosolized pentamidine, pyrimethamine and acyclovir. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to *RETROVIR* with these drugs.

## Pregnancy and Lactation

**Fertility:** There are no data on the effect of *RETROVIR* on human female fertility. In men, *RETROVIR* has not been shown to affect sperm count, morphology or motility.

**Pregnancy:** Zidovudine has been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 13,000 women during pregnancy and postpartum. Available human data from the APR do not show an increased risk of major birth defects for zidovudine compared to the background rate (*see Clinical Studies*).

The safe use of zidovudine in human pregnancy has not been established in adequate and well-controlled trials investigating congenital abnormalities. Therefore administration of *RETROVIR* in pregnancy should be considered only if the expected benefit outweighs the possible risk to the foetus.

Zidovudine has been shown to cross the placenta in humans (*see Pharmacokinetics*). Zidovudine has been associated with findings in animal reproductive studies (*see Pre-Clinical Safety Data*). Pregnant women considering using *RETROVIR* 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 *peri-partum* 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 *peri-partum* has not been established.

**Lactation:** Health experts recommend that where possible women infected with HIV do not breast feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

After administration of a single dose of 200 mg *RETROVIR* to HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum. In other studies following repeat oral dose of 300 mg zidovudine twice daily (given either as a single entity or as *COMBIVIR or TRIZIVIR*) the maternal plasma breast milk ratio ranged between 0.4 and 3.2. Zidovudine median infant serum concentration was 24 ng/ml in one study and was below assay limit of quantification (30 ng/ml) in another study. Intracellular zidovudine triphosphate (active metabolite of zidovudine) levels in breastfed infants were not measured therefor the clinical relevance of the serum concentration of the parent compound measured is unknown.

## Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *RETROVIR* on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless, the clinical status of the patient and the adverse event profile of *RETROVIR* should be borne in mind when considering the patient's ability to drive or operate machinery.

## Adverse Reactions

Only limited data are available in children with HIV infection.

The adverse event profile appears similar for adults and children. The following events have been reported in patients treated for *RETROVIR.*

The following convention has been utilised for the classification of undesirable effects: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

***Blood and lymphatic system disorders***

Common: Anaemia (which may require transfusions), neutropenia and leucopenia.

These 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), particularly in patients with CD4 cell counts less than 100/$mm^3$. Dosage reduction or cessation of therapy may become necessary (*see Warnings and Precautions*). This incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin $B_{12}$ levels were low at the start of *RETROVIR* therapy.

Uncommon: Thrombocytopenia and pancytopenia (with marrow hypoplasia).

Rare: Pure red cell aplasia.

Very rare: Aplastic anaemia.

***Metabolism and nutrition disorders***

Common: Hyperlactataemia.

Rare: Lactic acidosis (*see Warnings and Precautions*), anorexia.

Treatment with zidovudine has been associated with loss of subcutaneous fat (*see Warnings and Precautions*).

***Psychiatric disorders***

Rare: Anxiety and depression.

***Nervous system disorders***

Very common: Headache.

Common: Dizziness.

Rare: Insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions.

***Cardiac disorders***

Rare: Cardiomyopathy.

***Respiratory, thoracic and mediastinal disorders***

Uncommon: Dyspnoea.

Rare: Cough.

***Gastrointestinal disorders***

Very common: Nausea

Common: Vomiting, abdominal pain, and diarrhoea.

Uncommon: Flatulence.

Rare: Oral mucosa pigmentation, taste disturbance and dyspepsia. Pancreatitis.

***Hepatobiliary disorders***

Common: Raised blood levels of liver enzymes and bilirubin.

Rare: Liver disorders such as severe hepatomegaly with steatosis.

***Skin and subcutaneous tissue disorders***

Uncommon: Rash and pruritus.

Rare: Nail and skin pigmentation, urticaria and sweating.

***Musculoskeletal and connective tissue disorders***

Common: Myalgia.

Uncommon: Myopathy.

***Renal and urinary disorders***

Rare: Urinary frequency.

***Reproductive system and breast disorders***

Rare: Gynaecomastia.

***General disorders and administration site conditions***

Common: Malaise.

Uncommon: Fever, generalised pain and asthenia.

Rare: Chills, chest pain and influenza-like syndrome.

The available data from both placebo-controlled and open-labelled studies indicate that the incidence of nausea and other frequently reported clinical adverse events consistently decreases over time during the first few weeks of therapy with *RETROVIR*.

## Overdose

No specific symptoms or signs have been identified following acute overdose with *RETROVIR*, apart from those listed as undesirable effects such as fatigue, headache, vomiting, and occasional reports of haematological disturbances. Following a report where a patient took an unspecified

quantity of *RETROVIR*, blood zidovudine levels were over sixteen times the normal therapeutic level, but there were no short term clinical, biochemical or haematological sequelae identified.

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

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

# PHARMACOLOGICAL PROPERTIES

## Pharmacodynamics

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 act as an inhibitor of and substrate for the viral reverse transcriptase. The formation of further proviral DNA is blocked by incorporation of zidovudine-TP 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. No antagonistic effects in vitro were seen with zidovudine and other anti-retrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

Resistance to thymidine analogues (of which zidovudine is one) is well characterized 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 characterized by mutations in the HIV reverse transcriptase at codons 62, 75, 77, 116 and 151 and the second typically involving a T69S mutation plus a 6-pair insert at the same position, result in phenotypic resistance to zidovudine as well as the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

Reduced *in vitro* sensitivity to zidovudine has been reported for HIV isolates from patients who have received prolonged courses of *RETROVIR* 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 relationships between *in vitro* susceptibility of HIV to zidovudine and clinical response to therapy remain under investigation. *In vitro* susceptibility testing has not been standardized and results may therefore vary according to methodological factors.

Studies *in vitro* of zidovudine in combination with lamivudine indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resisitance to lamivudine. Evidence from clinical studies show that lamivudine plus zidovudine delays the emergence of zidovudine-resistant isolates in individuals with no prior anti-retroviral therapy.

Zidovudine has been used as a component of anti-retroviral combination therapy with other anti-retroviral agents of the same class (nucleoside reverse transcriptase inhibitors) or different classes (protease inhibitors, non-nucleoside reverse transcriptase inhibitors).

***Post-exposure prophylaxis (PEP):***

Internationally recognised guidelines (Centre for Disease Control and Prevention 2013), recommend that in the event of accidental exposure to HIV infected blood e.g. from a needle stick injury, a combination of zidovudine and lamivudine should be administered promptly (within one to two hours). In cases of higher risk of infection a protease inhibitor should be included in the regimen. It is recommended that antiretroviral prophylaxis be continued for four weeks. No controlled clinical studies have been carried out in post-exposure prophylaxis and supporting data is limited. Seroconversion may still occur despite prompt treatment with antiretroviral agents.

## Pharmacokinetics

### Pharmacokinetics in adults

### Absorption

Zidovudine is well absorbed from the gut and, at all dose levels studied, the bioavailability was 60-70%. From a Phase 1 study, mean steady state peak ($C_{ss}$max) and trough ($C_{ss}$min) plasma concentrations following oral administration of *RETROVIR* (in solution) at doses of 5mg/kg every 4 hours were 7.1 and 0.4µM (or 1.9 and 0.1µg/ml) respectively. From a bioequivalence study, mean $C_{ss}$max and $C_{ss}$min levels following oral administration of *RETROVIR* Capsules every 4 hours and dose normalised to 200mg were 4.5µM (1.2µg/ml) and 0.4µM (or 0.1µg/ml) respectively.

### Bioequivalence

*RETROVIR* Oral solution was shown, in patients, to be bioequivalent to *RETROVIR* Capsules in respect to the area under the zidovudine plasma concentration-time curve (AUC). The absorption of zidovudine following the administration of the oral solution was marginally faster than that following the administration of capsules, with mean times to peak concentrations of 0.5 and 0.8 hours respectively. Mean values for $C_{ss}$max, dose-normalised to 200mg were 5.8µM (or 1.55µg/ml) and 4.5µM (or 1.2µg/ml) for oral solution and capsules respectively. These data were generated using the US oral *RETROVIR* Syrup but can be considered to apply equally to *RETROVIR* Oral Solution.

**Distribution**

In adults, the average cerebrospinal fluid/plasma zidovudine concentration ratio 2-4 hours after dosing was found to be approximately 0.5. Data indicates that zidovudine crosses the placenta and is found in amniotic fluid and foetal blood. Zidovudine has also been detected in semen and milk.

In children the mean cerebrospinal fluid/plasma zidovudine concentration ratio ranged from 0.52-0.85, as determined during oral therapy 0.5-4 hours after dosing. During continuous intravenous infusion, the mean steady state cerebrospinal fluid/plasma concentration ratio was 0.24.

Plasma protein binding is relatively low (34-38%) and drug interaction involving binding site displacement are not anticipated.

**Metabolism**

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50 to 80% of the administered dose eliminated by renal excretion, 3'amino- 3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

**Elimination**

From studies with intravenous *RETROVIR*, the mean terminal plasma half-life was 1.1 hours, the mean total body clearance was 27.1 ml/min/kg and the apparent volume of distribution was 1.6 l/kg. Renal clearance of zidovudine greatly exceeds creatinine clearance, indicating that significant tubular secretion takes place. The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50-80% of the administered dose eliminated by renal excretion.

**Special Patient Populations**

**Children**

In children over the age of 5 to 6 months, the pharmacokinetic profile of zidovudine is similar to that in adults.

Zidovudine is well absorbed from the gut and, at all dose levels studies, its bioavailability was 60-74% with a mean of 65%. $C_{ss}$max levels were 4.45µM (1.19µg/ml) following a dose of 120mg *RETROVIR* (in solution)/$m^2$ body surface area and 7.7µM (2.06µg/ml) at 180mg/$m^2$ body surface area.

Concentrations of zidovudine in cerebrospinal fluid were measured after both intermittent oral and I.V. drug administration in 21 children during Phase I and Phase II studies. The mean zidovudine CSF/plasma concentration ratio measured at an average time of 2.2 hours post-dose at doses of 120 to 240 mg/$m^2$ was 0.52 ± 0.44 (n=28); after an injection of doses of 80 to 160 mg/$m^2$ over 1 hour, the mean CSF/plasma concentration ratio was 0.87 ± 0.66 (n=23) at 3.2 hours after the start of the infusion. During continuous intravenous infusion the mean steady-state CSF/plasma ratio was 0.26 ± 0.17 (n=28).

With intravenous dosing, the mean terminal plasma half-life and total body clearance were 1.5 hours and 30.9 ml/min/kg respectively. The major metabolite is the 5'-glucuronide. After intravenous dosing, 29% of the dose was recovered unchanged in the urine and 45% excreted as the glucuronide. Renal clearance of zidovudine greatly exceeds creatinine clearance indicating that significant tubular secretion takes place.

The data available on the pharmacokinetics in neonates and young infants indicate that glucuronidation of zidovudine is reduced with a consequent increase in bioavailablity, reduction in clearance and longer half-life in infants less than 14 days old but thereafter the pharmacokinetics appear similar to those reported in adults.

**Elderly**

The pharmacokinetics of zidovudine have not been studied in patients over 65 years of age.

**Renal Impairment**

Compared to healthy subjects, patients with advanced renal failure have a 50% higher peak plasma concentration of zidovudine. Systemic exposure (measured as area under the zidovudine concentration-time curve) is increased 100%; the half-life is not significantly altered. In renal failure there is substantial accumulation of the major, glucuronide metabolite but this does not appear to cause toxicity. Haemodialysis and peritoneal dialysis have no significant effect on zidovudine elimination whereas elimination of the glucuronide metabolite is increased (*see Dosage and Administration*).

**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*).

**Pregnancy**

The pharmacokinetics of zidovudine has been investigated in a study of eight women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of accumulation of zidovudine. The pharmacokinetics of zidovudine was similar to that of non-pregnant adults. Consistent with passive transmission of zidovudine across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery.

## Clinical Studies

The Antiretroviral Pregnancy Registry (APR) has received reports of over 13,000 exposures to 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 APR does not show an increased risk of major birth defects zidovudine compared to the background rate.

## Pre-clinical Safety Data

### Carcinogenicity, 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 *RETROVIR* than in those who had not. The clinical significance of these findings is unknown.

In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. There were no other zidovudine-related tumours observed in either sex of either species. A subsequent intravaginal carcinogenicity study confirmed 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. The predictive value of rodent carcinogenicity studies for humans is uncertain and thus the clinical significance of these findings is unclear.

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.

### Reproductive toxicology

Studies in pregnant rats and rabbits given zidovudine orally at dose levels up to 450 and 500 mg/kg/day respectively during the major period of organogenesis related no evidence of teratogenicity. There was, however, a statistically significant increase in foetal resorptions in rats given 150-450 mg/kg/day and in rabbits given 500 mg/kg/day. A separate study, reported subsequently, has shown that 3000 mg/kg/day (as two equal doses at least 6 hours apart) given to rats during the period of organogenesis, caused marked maternal toxicity and an increased incidence of foetal malformations. This dose is comparable to the single oral median lethal dose of 3683 mg/kg/day in the rat. No evidence of increased incidence of foetal abnormality was observed in this study at the lower dose rates administered – 600 mg/kg/day or less, also given as two equal doses.

Zidovudine did not impair male or female fertility in studies in rats.

# PHARMACEUTICAL PARTICULARS

## Shelf Life

The expiry date is indicated on the packaging.

## Special Precautions for Storage

Do not store above 30°C.

Keep *RETROVIR* capsules (100 mg and 250 mg) dry and protect from light.

Protect *RETROVIR* oral solution from light.

## Instructions for Use/Handling

The pack of *RETROVIR* Oral Solution contains an oral-dosing syringe.

It is recommended that this be used in preference to dilution of the product.

Not all presentations are available in every country.

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**Product Registrant**:

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