Plasma protein binding is relatively low (34-38%) and interactions with other active substances involving binding site displacement are not anticipated.

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).

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

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.

Bioequivalence:
In HIV-infected patients on **Retrovir** therapy, the 300 mg **Retrovir** tablet at steady state was bioequivalent to the 250 mg capsule, when adjusted for dose. As the kinetics of zidovudine are dose-independent following multiple dose oral administration, the 200 mg **Retrovir** tablets of identical formulation to the 300 mg tablet can also be considered bioequivalent to the 250 mg capsule after adjustment for dose.
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 200 mg were 5.8 microM (or 1.55 µg/ml) and 4.5 microM (1.2 µg/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.

Pharmaceutical Precautions and Recommendations
Retrovir Capsules 100 mg and 250 mg:- Do not store above 30°C. Keep dry. Protect from light.
Retrovir Tablets 300 mg:- Do not store above 30°C. Protect from light.
Retrovir Oral Solution/Syrup:- Do not store above 30°C.

List of Excipients
Retrovir capsules:
Capsule shell:
Titanium dioxide
Gelatin
Indigo carmine
Black iron oxide

Capsule contents:
Starches
Microcrystalline Cellulose
Sodium Starch Glycollate
Magnesium Stearate

Retrovir tablets:
Tablet core:
Microcrystalline Cellulose
Sodium Starch Glycollate
Povidone K30
Magnesium Stearate

Film coat:
Hypromellose
Titanium Dioxide
Macrogol

Polish:
Macrogol

Retrovir oral solution/syrup:
Hydrogenated Glucose Syrup
Glycerol
Citric Acid
Sodium Benzoate
Saccharin Sodium
Strawberry Flavour
White Sugar Flavour
Purified Water

Further Information:
Pre-clinical safety
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 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 unclear.
Carcinogenicity: 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 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. 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.
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.
Reproductive toxicology: Studies in pregnant rats and rabbits with zidovudine have shown increased incidences of early embryo deaths. A separate study in rats found that dosages very near the oral median lethal dose caused an increase in the incidence of foetal malformations. No evidence of teratogenicity has been observed at lower dosages tested.
Fertility: Zidovudine did not impair male or female fertility in studies in rats.

*Trade mark †Trade mark of Hoffman-La Roche Ltd Made in England

The Wellcome Foundation Ltd., London
94.05 MAS/9307/MRS/BQGT 93-10 Amendment BQGT 93-12 Amendment BQGT 93-14 50329GE1
Core Text Issue No. 18

Retrovir*
Oral Formulations

Wellcome

To the Medical and Pharmaceutical Professions.

Presentations
Not all presentations are registered in every country.
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
A pale yellow, strawberry-flavoured, sugar-free oral solution containing 50 mg Zidovudine in each 5 ml.
The pack contains a 10 ml oral-dosing syringe which should be fitted to the bottle before use and closed with the cap provided.

Indications
Not all indications are registered in every country.
Retrovir Oral Formulations are indicated in combination with other anti-retroviral agents for the management of patients with Human Immunodeficiency Virus (HIV) infection who are asymptomatic, or who have early symptoms associated with HIV disease progression.
Retrovir Oral Formulations are also indicated for the management of patients with advanced HIV disease, such as those with the Acquired Immune Deficiency Syndrome (AIDS) or AIDS-related complex (ARC).
Retrovir Oral Formulations are indicated for HIV infected children who have HIV-related symptoms or who are asymptomatic with markers indicating significant HIV-related immune suppression.
The benefit / risk assessments based on available data support early therapeutic intervention.

Dosage and Administration
Dosage in adults:
Retrovir therapy should be initiated by a physician experienced in the management of HIV infection.
Dosage in adults and adolescents over 12 years of age:
The recommended dose of **Retrovir** in combination with other anti- retroviral agents is 500 or 600 mg/day in two or three divided doses.
Dosages ≥ 1,000 mg in divided doses have been used in earlier clinical trials. The effectiveness of dosages lower than 1000 mg/day in the treatment or prevention of HIV- associated neurological dysfunction is unknown.
Dosage in children:
3 months - 12 years: The recommended dose of **Retrovir** is 360 to 480 mg/m^2 per day, in 3 or 4 divided doses in combination with other anti-retroviral agents. For the treatment or prevention of HIV-associated neurological dysfunction, the effectiveness of dosages less than 720 mg/m^2 per day (180 mg/m^2 every six hours) is unknown. The maximum dosage should not exceed 200 mg every 6 hours.
Less than 3 months: The limited data available are insufficient to propose specific dosage recommendations (See Maternal foetal transmission and Pharmacokinetic Properties).
Dosage in the prevention of maternal-foetal transmission
The following **Retrovir** dosage regimens have been shown to be effective (See Use During Pregnancy and Lactation):
- **ACTG076 study:** The recommended dose of **Retrovir** for pregnant women (over 14 weeks of gestation) is 500 mg/day orally (100 mg five times daily) until the beginning of labour. During labour and delivery **Retrovir** should be administered intravenously at 2 mg/kg bodyweight given over 1 hour, followed by a continuous intravenous infusion at 1 mg/kg/h until the umbilical cord is clamped.
  The newborn infants should be given **Retrovir** 2 mg/kg bodyweight orally every 6 hours starting within 12 hours after birth, and continuing until 6 weeks old. Infants unable to receive oral dosing should be given **Retrovir** intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours.
- **Thailand-Centers for Disease Control (CDC) study:** The recommended dose of **Retrovir** for pregnant women from week 36 of gestation is 300 mg **Retrovir** twice daily orally until onset of labour, and 300 mg **Retrovir** orally every three hours from onset of labour until delivery.

Dosage in renal impairment:
In patients with severe renal impairment daily dosages of 300 - 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 zidovudine 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 Pharmacokinetic Properties).
Dosage in 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. 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.
Dosage adjustments in patients with haematological adverse reactions:
Dosage reduction or interruption of **Retrovir** therapy may be necessary in patients whose haemoglobin 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 (see Contra-indications and Precautions and Warnings).
Dosage in the 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.

Contra-indications
Retrovir Oral Formulations are contra-indicated in patients known to be hypersensitive to zidovudine, or to any of the components of the formulations.
Retrovir Oral Formulations 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 7.5 g/dl or 4.65 mmol/l) (see Precautions and Warnings).

Precautions and Warnings
Patients should be cautioned about the concomitant use of self-administered medications (see Drug Interactions).
Patients should be advised that 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 indicate 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 disease (where bone marrow reserve is generally good), haematological adverse reactions are 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 disease (see Contra-indications).
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 alone or in combination, including zidovudine, in the treatment of HIV infection. A majority of these cases have been in women. Caution should be exercised when administering **Retrovir** to any patient, and particularly to those with known risk factors for liver disease. Treatment with **Retrovir** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Drug 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 medicinal products where caution should be exercised.
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 medicinal products.
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.
Ribavirin: The nucleoside analogue ribavirin antagonises the *in vitro* antiviral activity of zidovudine and so concomitant use of this active substance should be avoided.
Rifampicin: Limited data suggests that co-administration of zidovudine and rifampicin decreases AUC of zidovudine by 48% ± 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 zidovudine.
Miscellaneous: Other active substances 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 interactions before using such medicinal products, particularly for chronic therapy, in combination with **Retrovir**.
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 **Retrovir**. If concomitant therapy with any of these medicinal products 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.
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, aerosolised pentamidine, pyrimethamine and aciclovir. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to **Retrovir** with these medicinal products.

Pregnancy and Lactation
Pregnancy:
Zidovudine has been shown to cross the placenta in humans (see Pharmacokinetic Properties). Given the limited data available on the general use of **Retrovir** in pregnancy, the use of **Retrovir** prior to the 14th week of gestation should be considered only when the potential benefit to the mother outweighs the risk to the foetus (see Pre-clinical Safety Data).
Maternal-foetal transmission:
In ACTG-076 the use of **Retrovir** in pregnant women over 14 weeks of gestation, with subsequent treatment of their newborn infants, has been shown to significantly reduce the rate of maternal-foetal transmission of HIV (23% infection rate for placebo versus 8% for zidovudine). Oral **Retrovir** therapy began between weeks 14 and 34 of gestation and continued until onset of labour. During labour and delivery **Retrovir** was administered intravenously. The newborn infants received **Retrovir** orally until 6 weeks old. Infants unable to receive oral dosing were given the intravenous formulation.
In the 1998 Thailand CDC study, use of oral **Retrovir** therapy only, from week 36 of gestation until delivery, significantly reduced the rate of maternal-foetal transmission of HIV (19% infection rate for placebo versus 9% for zidovudine). No mothers in this study breast fed their infants.
It is unknown whether there are any long-term consequences of *in utero* and infant exposure to **Retrovir**. Based on the animal carcinogenicity/mutagenicity findings a carcinogenic risk to humans cannot be excluded (see Pre-clinical Safety Data). The relevance of these findings to both infected and uninfected infants exposed to **Retrovir** is unknown. However, pregnant women considering using **Retrovir** during pregnancy should be made aware of these findings.
Lactation:
Health experts recommend that where possible women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. After administration of a single dose of 200 mg zidovudine to HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum. Therefore, as zidovudine and the virus pass into breast milk it is recommended that mothers taking **Retrovir** do not breast feed their infants.
Fertility:
There are no data on the effect of **Retrovir** on human female fertility. In men, **Retrovir** has been shown to have no effect on sperm count, morphology or motility.

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 active substance. 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
The adverse event profile appears similar for adults and children. The following events have been reported in patients treated with **Retrovir**. They may also occur as part of the underlying disease process in association with other medicinal products used in the management of HIV disease. The relationship between these events and use of **Retrovir** is therefore difficult to evaluate, particularly in the medically complicated situations which characterise advanced HIV disease. A reduction in dose or suspension of **Retrovir** therapy may be warranted in the management of these conditions:-
Cardiovascular: - Cardiomyopathy.
Gastrointestinal tract: Nausea, vomiting, oral mucosa pigmentation, abdominal pain, dyspepsia, anorexia, diarrhoea, flatulence.
Haematological: Anaemia (which may require transfusions), neutropenia, leucopenia and aplastic anaemia. 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), and particularly in patients with CD_4 cell counts less than 100/mm^3. Dosage reduction or cessation of therapy may become necessary (see Precautions and Warnings). The 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.
Thrombocytopenia, pancytopenia (with marrow hypoplasia) and pure red cell aplasia.
Liver/pancreas: liver disorders such as severe hepatomegaly with steatosis, raised blood levels of liver enzymes and bilirubin, pancreatitis
Metabolic/endocrine: Lactic acidosis in the absence of hypoxaemia
Musculoskeletal: Myalgia, myopathy
Neurological/psychiatry: Headache, dizziness, insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions, anxiety, depression
Respiratory tract: Dyspnoea, cough
Skin: Nail and skin pigmentation, rash, urticaria, pruritus, sweating
Miscellaneous: Urinary frequency, taste perversion, fever, malaise, generalised pain, chills, chest pain, influenza-like syndrome, gynaecomastia, asthenia
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**.
Adverse reactions with Retrovir for the prevention of maternal-foetal transmission:-
In a placebo-controlled trial (ACTG 076), **Retrovir** was well tolerated in pregnant women at the doses recommended for this indication. Clinical adverse events and laboratory test abnormalities were similar in the **Retrovir** and placebo groups.
In the same trial, haemoglobin concentrations in infants exposed to **Retrovir** for this indication were marginally lower than in infants in the placebo group, but transfusion was not required. Anaemia resolved within 6 weeks after completion of **Retrovir** therapy. Other clinical adverse events and laboratory test abnormalities were similar in the **Retrovir** and placebo groups. The long-term consequences of *in utero* and infant exposure to **Retrovir** are unknown.

Overdosage
Symptoms and signs:
No specific symptoms or signs have been identified following acute overdose with zidovudine, 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 zidovudine, blood zidovudine levels were over sixteen times the normal therapeutic level, but there were no short term clinical, biochemical or haematological sequelae identified.
Treatment:
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.

Pharmacodynamic Properties
Pharmacotherapeutic group - nucleoside analogue - ATC Code J05A F01.
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-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.
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 **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 reduction of sensitivity and the emergence of zidovudine resistant strains limits the usefulness of monotherapy clinically. Studies *in vitro* of zidovudine in combination with lamivudine indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Furthermore *in vivo* there is clinical evidence that zidovudine plus lamivudine delays the emergence of zidovudine resistance in anti-retroviral naive patients.
Zidovudine has been shown to act additively or synergistically with a number of anti-HIV agents, such as lamivudine, didanosine, and interferon-α, inhibiting the replication of HIV in cell culture.
However, studies in-vitro indicate that triple combinations of nucleoside analogues or two nucleoside analogues and a protease inhibitor are more effective in inhibiting HIV-1 induced cytopathic effects than one or a combination of two medicinal products.
Post-exposure prophylaxis (PEP):
Internationally recognised guidelines (Centre for Disease Control and Prevention - June 1998), recommend that in the event of accidental exposure to HIV infected blood e.g. from a needlestick injury, a combination of **Retrovir** and Epivir™ 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.

Pharmacokinetic Properties
Adults:
Zidovudine is well absorbed from the gut and, at all dose levels studied, the bioavailability was 60-70%. From a Phase I 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 5 mg/kg every 4 hours were 7.1 and 0.4 microM (or 1.9 and 0.1 µg/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 200 mg were 4.5 microM (or 1.2 µg/ml) and 0.4 microM (or 0.1 µg/ml) respectively.
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. 3'amino- 3'- deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.
Children:
In children over the age of 5-6 months, the pharmacokinetic profile of zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and, at all dose levels studied, its bioavailability was 60-74% with a mean of 65%. C[ss]max levels were 4.45 microM (1.19 µg/ml) following a dose of 120 mg zidovudine (in solution)/m^2 body surface area and 7.7 microM (2.06 µg/ml) at 180 mg/m^2 body surface area.
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 bioavailability, 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.
Distribution:
In adults, the average cerebrospinal fluid/plasma zidovudine concentration ratio 2-4 hours after dosing was found to be approximately 0.5. Data indicate 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 and was 0.87 as determined during intravenous therapy 1-5 hours after a 1 hour infusion. During continuous intravenous infusion, the mean steady-state cerebrospinal fluid/plasma concentration ratio was 0.24.