RETROVIR
Zidovudine

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

CLINICAL INFORMATION

Indications

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

RETROVIR is indicated for use in HIV-positive pregnant women and their newborn infants as it has been shown to reduce the rate of maternal-foetal transmission of HIV (*see Pregnancy and Lactation*).

Dosage and Administration

Pharmaceutical form:
Oral solution.

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

- **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.

- **Children**

Oral solution:

Children weighing at least 9 kg and less than 30 kg:
The recommended dose of *RETROVIR* is 0.9 mL/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 (30 mL) twice daily.

Children weighing at least 4 kg and less than 9 kg:
The recommended dose of *RETROVIR* is 1.2 mL/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 Prevention of maternal foetal transmission 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 h (*see Pharmacokinetics*).

- **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.

- **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 Contraindications, Warnings and Precautions*).

- **Prevention of maternal-foetal transmission**

The following *RETROVIR* dosage regimens have been shown to be effective (*see Pregnancy and Lactation*).

  – *ACTG 076 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 h, followed by a continuous i.v. infusion at 1 mg/kg/h until the umbilical cord is clamped.

Neonates should be given *RETROVIR* 0.2 mL/kg (2 mg/kg) bodyweight of oral solution every 6 h starting within 12 h after birth, and continuing until six weeks old.

An appropriate sized syringe with 0.1 mL graduation should be used to ensure accurate dosing of neonates.

Table 1: Examples of Neonatal Dosing Recommendations for Retrovir Oral Solution for the Prevention of Mother to Child Transmission (PMTCT) of HIV in Neonates.

Neonate Body Weight in kilograms (kg)	**Total volume of dose in millilitres (mL)** 0.2mL/kg	**How often should each dose be taken (in 24 hours)**	**Dose of zidovudine in milligrams (mg)** 2mg/kg
2.0 kg	**0.4 mL**	**4 times**	4 mg
5.0 kg	**1.0 mL**	**4 times**	10 mg

Infants unable to receive oral dosing should be given *RETROVIR* infusion intravenously at 1.5 mg/kg bodyweight infused over 30 min every 6 h.

Contraindications

RETROVIR is contraindicated in patients known to be hypersensitive to zidovudine, or to any of the components 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 7.5 g/dl or 4.65 mmol/l) (*see Warnings and Precautions*).

Warnings and Precautions

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

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

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 two weeks for the first three 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 one to three 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 to 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 in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised 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 factors for liver disease. Treatment with *RETROVIR* should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

- ***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 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 medicinal products 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 avoided 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 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.

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 *RETROVIR*.

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 of oral *RETROVIR* do not indicate a significantly increased risk of adverse reactions to *RETROVIR* with these medicinal products.

Pregnancy and Lactation

Fertility

There are no data on the effect of *RETROVIR* on human female fertility. In men, zidovudine has been shown to have no effect on 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 Non-Clinical Information*). 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. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Maternal-foetal transmission

In study 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 *RETROVIR*). 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 i.v. 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 *RETROVIR*). 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 zidovudine. Based on the animal carcinogenicity/mutagenicity findings a carcinogenic risk to humans cannot be excluded (*see Non-Clinical Information*). The relevance of these findings to both infected and uninfected infants exposed to zidovudine 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. 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 therefore the clinical relevance of the serum concentrations 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 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*.

The following convention has been utilised for the classification of undesirable effects: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), 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 (1200-1500mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts less than 100/mm^3. Dosage reduction or cessation of therapy may become necessary (*see Warnings and Precautions*). 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.

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.

Hepatobilary 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*.

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.

Overdose

Symptoms and Signs

No specific symptoms or signs have been identified following acute overdose with *RETROVIR*, apart from those listed as undesirable effects.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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 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.

Clinical virology:
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 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 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.

No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

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 typically 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 the US ACTGO76 trial, Retrovir 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 a day) 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 Retrovir 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 regimens 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.

Pharmacokinetics

Absorption

Zidovudine is well absorbed from the gut and, at all dose levels studied, the bioavailability was 60 to 70%. From a Phase I study, mean steady state peak (C[ss]max) and trough (C[ss]min) plasma concentrations following oral administration of zidovudine (in solution) at doses of 5 mg/kg every 4 h were 7.1 and 0.4 micromol (or 1.9 and 0.1 micrograms/ml) respectively. From a bioequivalence study, mean C[ss]max and C[ss] min levels following oral administration of zidovudine capsules every 4 h and dose normalised to 200 mg were 4.5 micromol (or 1.2 micrograms/ml) and 0.4 micromol (or 0.1 micrograms/ml) respectively.

- **Bioequivalence**

In HIV-infected patients on zidovudine therapy, the 300 mg zidovudine 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 *RETROVIR* 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 h respectively. Mean values for C[ss]max, dose-normalised to 200 mg were 5.8 micromol (or 1.55 micrograms/ml) and 4.5 micromol (1.2 micrograms/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.

Solution for infusion:

Dose-independent kinetics were observed in patients receiving 1 h infusions of 1 to 5 mg/kg three to six times daily. Mean steady state peak (C_{ss}max) and trough (C_{ss}min) plasma concentrations in adults following a 1 h infusion of 2.5 mg/kg every 4 h were 4.0 and 0.4 micromol respectively (or 1.1 and 0.1 micrograms/ml).

Distribution

From studies with i.v. zidovudine, the mean terminal plasma half- life was 1.1 h, the mean total body clearance was 27.1 ml/min/kg and the apparent volume of distribution was 1.6 l/kg.

In adults, the average cerebrospinal fluid/plasma zidovudine concentration ratio 2 to 4 h 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.

Plasma protein binding is relatively low (34 to 38%) and interactions with other active substances 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 i.v. dosing.

Elimination

Renal clearance of zidovudine greatly exceeds creatinine clearance, indicating that significant tubular secretion takes place.

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 studied, its bioavailability was 60 to 74% with a mean of 65%. C[ss]max levels were 4.45 micromol (1.19 micrograms/ml) following a dose of 120 mg zidovudine (in solution)/m^2 body surface area and 7.7 micromol (2.06 micrograms/ml) at 180 mg/m^2 body surface area.

In children, the mean cerebrospinal fluid/plasma zidovudine concentration ratio ranged from 0.52 to 0.85, as determined during oral therapy 0.5 to 4 h after dosing and was 0.87 as determined during i.v. therapy 1 to 5 h after a 1 h infusion. During continuous i.v. infusion, the mean steady-state cerebrospinal fluid/plasma concentration ratio was 0.24.

With i.v. dosing, the mean terminal plasma half-life and total body clearance were 1.5 h and 30.9 ml/min/kg respectively. The major metabolite is the 5'-glucuronide. After i.v. 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.

- **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.

NON-CLINICAL INFORMATION

- **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. A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking *RETROVIR* as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. The clinical significance of these findings is unknown.

- **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 (420mg/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.

PHARMACEUTICAL INFORMATION

List of Excipients

RETROVIR oral solution:
hydrogenated glucose syrup, glycerol, citric acid, sodium benzoate, saccharin sodium, strawberry flavour, white sugar flavour, purified water.

Shelf Life

The expiry date is indicated on the packaging.

***RETROVIR* oral solution**
Discard 1 month after first opening.

Storage

The storage conditions are indicated on the packaging. Protect from light.

Nature and Contents of Container

RETROVIR oral solution:	amber glass bottle with a child resistant high density polyethylene outer cap and inner polypropylene cap with a polyethylene wad, with either a 1 mL or 10 mL oral-dosing syringe in the pack which should be fitted to the bottle before use. *RETROVIR* oral solution is supplied in bottles of 200mL.

Incompatibilities

None known.

Use and Handling

1. Remove the plastic wrap from the syringe/adapter.
2. Remove the adapter from the syringe.
3. **Remove the bottle cap** and keep it safely
4. **Push the plastic adapter into the neck of the bottle,** while holding the bottle firmly.
5. **Insert syringe** firmly into adapter

6. **Turn the bottle** upside down
7. **Pull out syringe plunger** until the first portion of your full dose is withdrawn
8. **Turn the bottle the right way up** and remove the syringe from the adapter
9. **Put the syringe into your mouth, Slowly push the plunger in** and repeat above steps **until you have taken the whole dose.**
10. Take the syringe and the adapter off and wash them thoroughly in clean water and dry completely before you use them again.
11. **Close the bottle** tightly with the cap

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