

DATA SHEET

RETROVIR[®] Oral Formulations

Zidovudine (AZT) 100mg capsules

Zidovudine (AZT) 10mg/mL oral solution

Presentation

Retrovir 100mg Capsules: Opaque white cap and body coded GSYJU. Containing 100mg zidovudine.

Retrovir oral solution/syrup: A clear, pale yellow, strawberry-flavoured, sugar-free oral solution. The pack contains a 10mL oral-dosing syringe, which should be fitted to the bottle before use and closed with the cap provided. Containing 50mg zidovudine per 5mL.

Uses

Actions

Pharmacotherapeutic group - nucleoside analogue.

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. 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.

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 zidovudine as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

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 standardised 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 resistance 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 widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (nucleoside reverse transcriptase inhibitors) or different classes (protease inhibitors, non-nucleoside reverse transcriptase inhibitors).

Pharmacokinetics

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 5mg/kg every 4 hours were 7.1 and 0.4microM (or 1.9 and 0.1mcg/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 4.5microM (or 1.2mcg/mL) and 0.4microM (or 0.1mcg/mL) respectively.

From studies with intravenous Retrovir, the mean terminal plasma half-life was 1.1 hours, the mean total body clearance was 27.1mL/min/kg and the apparent volume of distribution was 1.6L/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- 2'- 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_{max} levels were 4.45µM (1.19mcg/mL) following a dose of 120mg zidovudine (in solution)/m² body surface area and 7.7µM (2.06mcg/mL) at 180mg/m² body surface area.

With intravenous dosing, the mean terminal plasma half-life and total body clearance were 1.5 hours and 30.9mL/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.

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: 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 5.8microM (or 1.55mcg/mL) and 4.5microM (1.2mcg/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.

Indications

Retrovir Oral Formulations are 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

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

Dosage in adults and adolescents weighing at least 30kg:

The recommended dose of Retrovir in combination with other anti-retroviral agents is 250 or 300 mg twice daily. Dosages \geq 1,000mg in divided doses have been used in earlier clinical trials. The effectiveness of dosages lower than 1000mg/day in the treatment or prevention of HIV-associated neurological dysfunction is unknown.

Dosage in children:

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

The recommended dose of Retrovir is 9mg/kg twice daily in combination with other anti-retroviral agents. For those patients where zidovudine is being used for the treatment or prevention of HIV-associated neurological dysfunction, the effectiveness of dosages less than 720mg/m² per day (approximately 18mg/kg twice daily) is unknown. The maximum dosage should not exceed 300mg twice daily

Children weighing at least 4 kg and less than 9 kg: The recommended dose of zidovudine is 12 mg/kg twice daily in combination with other antiretroviral agents. Available data are insufficient to propose specific dosage recommendations for children weighing less than 4kg (See below -maternal foetal transmission and Pharmacokinetics).

Dosage in the prevention of maternal-foetal transmission:

The following Retrovir dosage regimens have been shown to be effective (See Pregnancy and Lactation):

- *ACTG076 study:* The recommended dose of Retrovir for pregnant women (over 14 weeks of gestation) is 500mg/day orally (100mg five times daily) until the beginning of labour. During labour and delivery Retrovir should be administered intravenously at 2mg/kg bodyweight given over 1 hour, followed by a continuous intravenous infusion at 1mg/kg/h until the umbilical cord is clamped. The newborn infants should be given Retrovir 2mg/kg bodyweight of oral solution 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 infusion intravenously at 1.5mg/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 300mg Retrovir twice daily orally until onset of labour, and 300mg 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 - 400mg 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 100mg every 6 to 8 hours. (See Pharmacokinetics)

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 7.5g/dL (4.65mmol/L) and 9g/dL (5.59mmol/L) or whose neutrophil count falls to between $0.75 \times 10^9/L$ and $1.0 \times 10^9/L$ (see Contraindications and Warnings and Precautions).

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.

Contraindications

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 $0.75 \times 10^9/L$) 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 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 (1200-1500mg/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 7.5g/dL (4.65mmol/L) and 9g/dL (5.59mmol/L) or the neutrophil count falls to between $0.75 \times 10^9/L$ and $1.0 \times 10^9/L$, 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 reinstated. 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 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 (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Fat redistribution:

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting and breast enlargement, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy (see Adverse Effects).

Whilst all members of the PI and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risk between individual members of the respective therapeutic classes.

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome: 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 jirovecii (P. carinii) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

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.

Pregnancy and Lactation

Pregnancy: Zidovudine has been shown to cross the placenta in humans (See Pharmacokinetics). 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 Preclinical Safety Data).

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 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 Preclinical 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 200mg 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.

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 area under the plasma concentration-time curve 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 $48\% \pm 34\%$. 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 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 (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 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.

Adverse Effects

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:-

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/mm³. Dosage reduction or cessation of therapy may become necessary (see Special Warnings and Special Precautions for Use). The incidence of neutropenia was also increased in those patients whose

neutrophil counts, haemoglobin levels and serum vitamin B₁₂ 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 Special Warnings and Special Precautions for Use), anorexia.

Redistribution/accumulation of body fat (see Special Warnings and Special Precautions for Use). The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

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.

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 Effects) 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.

Pharmaceutical Precautions

Incompatibilities

None known.

Shelf Life

Retrovir Capsules 100mg: 5 years.

Retrovir Oral Solution/Syrup: 2 years.

Special Precautions for Storage

Retrovir Capsules 100mg: Store below 30°C. Keep dry. Protect from light.

Retrovir Oral Solution/Syrup: Store below 30°C.

Instructions for use/handling

No special instructions are required.

Medicines Classification

Prescription Only Medicine

Package Quantities

Retrovir Capsules 100mg: Bottle or blister containing 100 capsules.

Retrovir Oral Solution/Syrup: 200mL amber glass bottle with either metal or plastic cap and polyethylene wad, with a 10mL oral-dosing syringe in the pack which should be fitted to the bottle before use.

Further Information

Preclinical Safety Data

Mutagenicity: No evidence of mutagenicity was observed in the Ames test. However, zidovudine was weakly mutagenic in a mouse lymphoma cell assay and was positive in an *in vitro* cell transformation assay. Clastogenic effects were observed in an *in vitro* study in human lymphocytes and *in 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 zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. The clinical significance of these findings is unknown.

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 40mg/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.

List of Excipients

Retrovir capsules:

Capsule shell: Titanium dioxide, Gelatin, Opacode S-1-27794 Black (contains Black iron oxide)

Capsule contents: Starches, Microcrystalline Cellulose, Sodium Starch Glycollate, Magnesium Stearate

Retrovir oral solution/syrup:

Hydrogenated Glucose Syrup, Glycerol, Citric Acid, Sodium Benzoate, Saccharin Sodium, Strawberry Flavour, White Sugar Flavour, Purified Water.

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 3TC™ 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.

Name and Address

GlaxoSmithKline NZ Ltd
AMP centre
Cnr Albert & Customs Streets
Private Bag 106600
Downtown Auckland
NEW ZEALAND

Phone: (09) 367 2900
Facsimile: (09) 367 2910

Date of Preparation

Date of preparation: 30 November 2010

Version: 2.0

Retrovir® is a registered trade mark of the GlaxoSmithKline group of companies.

© This data sheet is copyrighted to GlaxoSmithKline and may be reproduced but not altered in any way.