# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

RETROVIR I.V. for Infusion.

*Zidovudine10 mg/mL*

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RETROVIR I.V. for Infusion vials contain 200 mg of zidovudine in 20 mL solution (10 mg zidovudine/mL).

## 3. PHARMACEUTICAL FORM

Solution for infusion.

RETROVIR I.V. for Infusion is a clear, nearly colourless, sterile aqueous solution with a pH of approximately 5.5.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

RETROVIR I.V. for Infusion is indicated for the short-term management of serious manifestations of Human Immunodeficiency Virus (HIV) infection in patients with Acquired Immune Deficiency Syndrome (AIDS), who are unable to take RETROVIR Oral Formulations.

RETROVIR is indicated for use in HIV-positive pregnant women (over 14 weeks of gestation) and their newborn infants, as it has been shown to reduce the rate of maternal-foetal transmission of HIV (see section 4.6 Fertility, pregnancy and lactation).

### 4.2 Dose and method of administration

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

The required dose of RETROVIR I.V. for Infusion must be administered by slow intravenous infusion of the diluted product **over a one-hour period**.

RETROVIR I.V. for Infusion must **NOT** be given intramuscularly.

*Dilution:* RETROVIR I.V. for Infusion **must** be diluted prior to administration (see section 4.2 Dose and method of administration, Method of administration).

Patients should receive RETROVIR I.V. for Infusion only until oral therapy can be administered.

## Dose

### Dosage in adults and adolescents weighing at least 30kg:

A dosage of RETROVIR I.V. for Infusion of 1 or 2 mg zidovudine/kg every four hours provides similar exposure (AUC) to an oral dosage of 1.5 or 3 mg zidovudine/kg every four hours (600 or 1200 mg/day for a 70 kg patient).

### Dosage in children:

*3 months-12 years:*
Limited data are available on the use of RETROVIR I.V. for Infusion in children. A range of dosages between 80 and 160 mg/m$^2$ body surface area every 6 hours (320-640 mg/m$^2$/day) have been used. However, estimated exposure following doses of between 240-320 mg/m$^2$ per day in 3 or 4 divided doses would approximately correspond to the currently recommended oral dose of 360 to 480 mg/m$^2$ per day, although there is no efficacy data currently available on these lower intravenous doses.

*Less than 3 months:*
Available data are insufficient to propose specific dosage recommendations (see below – Dosage in the prevention of maternal-foetal transmission and section 5.2 Pharmacokinetic properties).

### Dosage in the prevention of maternal-foetal transmission:

The following dosage regimen has been shown to be effective. Pregnant women (over 14 weeks of gestation) should be given 500 mg/day orally (100mg 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 2 mg/kg bodyweight of oral solution every 6 hours starting within 12 hours after birth and continuing until 6 weeks old. An appropriate syringe should be used to ensure accurate dosing of infants. Infants unable to receive oral dosing should be given RETROVIR infusion intravenously at 1.5mg/kg bodyweight infused over 30 minutes every 6 hours.

## Special populations

### Dosage in renal impairment:

In patients with severe renal impairment, the recommended intravenous dosage is 1 mg/kg 3-4 times daily. This is equivalent to the current recommended oral daily dosage for this patient group of 300-400 mg allowing for oral bioavailability of 60-70%. 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 section 5.2 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 section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

**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.

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**Method of administration**

RETROVIR I.V. for Infusion **must** be diluted prior to administration.

Since no antimicrobial preservative is included, dilution must be carried out under full aseptic conditions, preferably immediately prior to administration, and any unused portion of the vial should be discarded.

The required dose should be added to and mixed with Glucose Intravenous Infusion 5% w/v to give a final zidovudine concentration of either 2 mg/mL or 4

mg/mL. These dilutions are chemically and physically stable for up to 48 hours at both 5°C and 25°C.

Should any visible turbidity appear in the product either before or after dilution or during infusion, the preparation should be discarded.

## 4.3 Contraindications

RETROVIR I.V. for Infusion is contraindicated in patients known to be hypersensitive to zidovudine, or to any of the components of the formulation.

RETROVIR I.V. for Infusion 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 section 4.4 Special warnings and precautions for use).

## 4.4 Special warnings and precautions for use

Patients should be cautioned about the concomitant use of self-administered medications (see section 4.5 Interactions with other medicines and other forms of interactions).

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 high 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. It is generally recommended that blood tests are performed at least weekly in patients receiving RETROVIR I.V. for Infusion.

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. Data on the use of intravenous RETROVIR for periods in excess of 2 weeks are limited. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (see section 4.3 Contraindications).

**Lactic acidosis and 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 or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

**Lipoatrophy**

Treatment with zidovudine has been associated with loss of subcutaneous fat. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs and buttocks, may be only partially reversible and improvement may take several months when switching to a zidovudine-free regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine and other zidovudine containing products (COMBIVIR and TRIZIVIR), and if feasible therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

**Serum lipids and blood glucose**

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

**Immune Reconstitution Syndrome (IRIS)**

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical

conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* (*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

**Patients co-infected with hepatitis C virus**

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. Therefore, the co-administration of ribavirin and zidovudine is not advised and consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This is particularly important in patients with a known history of zidovudine induced anaemia.

**Latex allergy**

The rubber stopper of the zidovudine i.v. for infusion vials contains dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

## 4.5 Interaction with other medicines and other forms of interaction

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.

**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 medicines (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 medicines 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 medicines.

## 4.6 Fertility, pregnancy and lactation

**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 section 5.1 Pharmacodynamic properties, Clinical efficacy and safety).

The safe use of zidovudine in human pregnancy has not been established in adequate and well-controlled trials investigating congenital abnormalities. Therefore, administration of zidovudine 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 section 5.2 Pharmacokinetic properties). Zidovudine has been associated with findings in animal reproductive studies (see section 5.3 Preclinical Safety Data). Pregnant women considering using zidovudine 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 ACTG 076 study, 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 in 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.

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 section 5.3 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.

**Breast-feeding**

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 zidovudine 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.

**Fertility**

There are no data on the effect of RETROVIR on human female fertility. In men, oral RETROVIR has been shown to have no effect on sperm count, morphology or motility.

### 4.7 Effects on ability to drive and use machines

RETROVIR I.V. for Infusion is generally used in an in-patient hospital population and information on ability to drive and use machinery is not usually relevant. 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.

## 4.8 Undesirable effects

### Summary of safety profile

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 medicines 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.

### Tabulated list of adverse reactions

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 (1200-1500 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 section 4.4 Special warnings and precautions for use). 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 section 4.4 Special warnings and precautions for use), anorexia. Treatment with zidovudine has |

been associated with loss of subcutaneous fat (see section 4.4 Special warnings and precautions for use).

*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

Experience with RETROVIR I.V. for Infusion treatment for periods in excess of two weeks is limited, although some patients have received treatment for up

to 12 weeks. The most frequent adverse events were anaemia, neutropenia, and leucopenia. Local reactions were infrequent.

The available data from studies of RETROVIR Oral Formulations 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 six 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.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting/

## 4.9 Overdose

**Symptoms and signs:**

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

**Treatment:**

Patients should be observed closely for evidence of toxicity (see section 4.8 Undesirable 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group - nucleoside analogue.

### Mechanism 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 a substrate for the viral reverse transcriptase. The formation of further proviral DNA is blocked by incorporation of zidovudine-MP into the chain and subsequent chain termination. Competition by zidovudine-TP for HIV reverse transcriptase is approximately 100-fold greater than for cellular DNA polymerase alpha. No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

### Pharmacodynamic effects

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).

**Clinical efficacy and safety**

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.

## 5.2 Pharmacokinetic properties

**Absorption**

Dose-independent kinetics were observed in patients receiving one-hour infusions of 1-5mg/kg three to six times daily. Mean steady state peak ($C_{[ss]max}$) and trough ($C_{[ss]min}$) plasma concentrations in adults following a one-hour infusion of 2.5 mg/kg every 4 hours were 4.0 and 0.4 microM respectively (or 1.1 and 0.1 mcg/mL).

**Distribution**

From studies with IV zidovudine, 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.

In adults, the average cerebrospinal fluid/plasma zidovudine concentration ratio 2-4 hours after oral 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 (34-38%) 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 50-80% of the administered dose eliminated by renal excretion. 3'amino-3'- deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

**Elimination**

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

**Special patient populations**

**Children**

In children over the age of 5-6 months, the pharmacokinetic profile of zidovudine is similar to that in adults. $C_{[ss]max}$ levels were 1.46 mcg/mL following an intravenous dose of 80 mg zidovudine/$m^2$ body surface area, 2.26 mcg/mL following 120 mg/$m^2$ and 2.96 mcg/mL following 160 mg/$m^2$.

In children, the mean cerebrospinal fluid/plasma zidovudine concentration ratio was 0.87 as determined during intravenous therapy 1-5 hours after a 1 hour infusion. The mean steady state ratio during continuous intravenous infusion was 0.24.

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.

**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 section 4.2 Dose and method of 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 section 4.2 Dose and method of 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 the medicine across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery.

## 5.3 Preclinical safety data

### Mutagenicity

No evidence of mutagenicity was observed in the Ames test. However, zidovudine was weakly mutagenic in a mouse lymphoma cell assay and was positive in an *in vitro* cell transformation assay. Clastogenic effects were observed in an *in vitro* study in human lymphocytes and *in 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 oral 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 (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses of 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.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Hydrochloric acid

Sodium hydroxide

Water for injection.

## 6.2 Incompatibilities

No data.

## 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store below 30°C. Protect from light.

### 6.5 Nature and contents of container

Amber glass vial containing 20 mL.

Boxes of 5 vials.

### 6.6 Special precautions for disposal

No special requirements

## 7. MEDICINE SCHEDULE

Prescription Only Medicine

## 8. SPONSOR

GlaxoSmithKline NZ Ltd
Private Bag 106600
Downtown Auckland
NEW ZEALAND

Phone: (09) 367 2900
Facsimile: (09) 367 2506

## 9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 17 December 1992

## 10. DATE OF REVISION OF THE TEXT

20 March 2025

**Summary table of changes:**

| Section changed | Summary of new information |
|---|---|
| 4.4 | Inclusion of latex allergy warning |

Version: 10.0