RETROVIR IV

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

RETROVIR IV

Zidovudine 200 mg/20 mL

Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 20 mL contains zidovudine 200 mg

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Concentrate for solution for infusion.

A clear, colourless or pale-yellow, sterile aqueous solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

RETROVIR IV is indicated for the short-term management of serious manifestations of Human Immunodeficiency Virus (HIV) infections in patients who are unable to take zidovudine oral formulations.

RETROVIR IV is indicated in pregnancy to reduce the rate of maternal-foetal transmission of HIV.

4.2 Posology and method of administration:

The required dose of RETROVIR IV must be administered by slow intravenous infusion over a one-hour period. It must NOT be given intramuscularly.

Dilution: RETROVIR IV must be diluted prior to administration (see section 6.6).

Dosage in adults:

A dose of RETROVIR IV for infusion of 1,9 mg zidovudine/kg every 4 hours (or 800 mg/day) is generally recommended for a 70 kg patient. This provides similar exposure (AUC) to an oral dose of approximately 2,9 mg zidovudine/kg every 4 hours (or 1 200 mg/day) for a 70 kg patient. Patients should receive RETROVIR IV for infusion only until oral therapy can be administered.

In individual cases, medical practitioners may wish to select a lower dosage, depending on relevant factors such as the degree of bone marrow reserve of the patient.

Dosage adjustments in patients with haematological toxicity:

Dosage reduction or interruption of zidovudine 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.

Dosage in children:

Limited data are available on the use of RETROVIR IV in children.

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 (100 mg five times/daily) until the beginning of labour. During labour and delivery RETROVIR IV should be administered intravenously at 2 mg/kg

bodymass 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 zidovudine 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 IV infusion intravenously at 1,5 mg/kg bodyweight infused over 30 minutes every 6 hours.

Dosage in the elderly:

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. Special care is advised in this age group due to age-associated changes such as decrease in renal function and alterations in haematological parameters. Appropriate monitoring of patients before and during use of RETROVIR IV is advised.

Dosage in renal impairment:

Compared to healthy subjects, patients with renal failure (creatinine clearance <10 mL/min) have a 50 % higher maximum 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.

In patients with severe renal impairment on peritoneal or haemodialysis daily dosages of 300-400 mg in 3-4 divided dosages 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 elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

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. Medical practitioners will need to monitor for signs of intolerance and adjust the dose and/or increase the interval between doses as appropriate.

4.3 Contraindications:

RETROVIR IV is contraindicated in patients known to be hypersensitive to zidovudine, or to any components of the formulation listed in section 6.1. RETROVIR IV should not be given to patients with abnormally low neutrophil cell counts (less than 0,75 x 10^9/litre) or abnormally low haemoglobin levels (less than 7,5 g/dL).

There is a known interaction between zidovudine and stavudine (d4T) (see section 4.5). The concomitant use of these two medicines should be avoided.

4.4 Special warnings and precautions for use:

Patients should be cautioned about the concomitant use of self-administered medications (see section 4.5). RETROVIR IV contains no preservative. Dilution should be carried out immediately before use and any unused solution should be discarded.

RETROVIR IV 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 risk of opportunistic infections, data on the development of neoplasms, including lymphomas are limited.

Pregnant women considering the use of zidovudine during pregnancy and labour for prevention of HIV transmission to their infants should be advised that transmission may still occur despite therapy.

Lactic acidosis/hyperlactataemia:

Use of RETROVIR IV can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of anti-retroviral nucleoside analogues including RETROVIR IV, either alone or in combination, in the treatment of HIV infection. A majority of these cases have been in women.

Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/L with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes (e.g., sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.)
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering RETROVIR IV to patients with known risk factors for liver disease. Treatment with RETROVIR IV 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).

Mitochondrial dysfunction*:*

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia) and peripheral neuropathy. Some late-onset

neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis:

Pancreatitis has been observed in some patients receiving RETROVIR IV. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of RETROVIR IV until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of zidovudine is increased due to decreased clearance. The dose of RETROVIR IV should therefore be adjusted (see section 4.2).

Liver disease:

Use of RETROVIR IV can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of RETROVIR IV has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Lipoatrophy:

Treatment with RETROVIR IV 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, 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 lifestyle 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:

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 tuberculosis, cytomegalovirus retinitis, other generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* pneumonia (PJP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Grave's 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 with HIV and hepatitis B or C virus co-infection:

Patients with chronic hepatitis B or C and treated with anti-retroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue RETROVIR IV should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post treatment exacerbation of hepatitis may lead to hepatic decompensation.

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

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections:

Patients receiving RETROVIR IV should be advised that they may continue to develop opportunistic infections and other complications of HIV infection and therefore they should remain

under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Haematological side effects:

Anaemia (usually occurring after six weeks of therapy but occasionally earlier), neutropenia (usually occurring at any time after 4 weeks' therapy but sometimes earlier) and leucopenia (usually secondary to neutropenia) can be expected to occur frequently in patients receiving RETROVIR. These occurred more frequently at higher dosages (1 200-1 500 mg/day) and in patients with poor bone marrow reserve prior to treatment and 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 IV 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 IV therapy at a reduced dosage may be re-instituted. Data on the use of RETROVIR IV 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).

Reproductive toxicology:

In animal studies, zidovudine was shown to cross the placenta and have demonstrated evidence of causing an increase in early embryonic deaths in rats and rabbits. Zidovudine given to rats during

organogenesis resulted in an increased incidence of malformations. RETROVIR should not be used in the first trimester of pregnancy.

Prevention of maternal-foetal transmission:

In placebo-controlled trials, haemoglobin concentrations in infants exposed to RETROVIR IV for this indication were lower than in infants in the placebo group, but transfusion was not required. Anaemia resolved within 6 weeks after completion of RETROVIR IV therapy. The long-term consequences of in utero and infant exposure to RETROVIR IV are unknown.

Latex allergy:

The rubber stopper of the RETROVIR IV vials contains dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

Sodium:

RETROVIR IV contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction:

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. Medicines 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 medicine where caution should be exercised.

Atovaquone: RETROVIR IV 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

RETROVIR IV 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 (*Pneumocystitis carinii/jirovecii* pneumonia) would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of RETROVIR IV. 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 RETROVIR IV and clarithromycin by at least two hours.

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

Stavudine: RETROVIR IV may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. RETROVIR IV is therefore not recommended to be used in combination with stavudine (see section 4.3).

Probenecid: Limited data suggest that probenecid increases the mean half-life and area under the plasma concentration curve of zidovudine by decreasing glucuronidation. Probenecid increases the AUC of zidovudine by 106 % (range 100 to 170 %). Patients receiving both drugs should be closely monitored for haematological toxicity. Renal excretion of the glucuronide (and possibly zidovudine itself) is reduced in the presence of probenecid.

Rifampicin: Limited data suggests that co-administration of RETROVIR IV and rifampicin decreases the AUC of zidovudine by 48 % ± 34 %. This may result in a partial loss or total loss of efficacy of zidovudine. The concomitant use of rifampicin with zidovudine should be avoided.

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.

Miscellaneous: Other medicines (such as 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 medicines interactions before using such medicines, particularly for chronic therapy, in combination with RETROVIR IV for infusion.

Concomitant therapy with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of toxicity with RETROVIR IV for infusion. 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 medicines should be reduced.

Since some patients receiving zidovudine may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such therapy has included co-trimoxazole, aerosolised pentamidine, pyrimethamine and acyclovir. Limited data from clinical trials do not indicate a significantly increased risk of toxicity 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).

The safe use of zidovudine in human pregnancy has not been established in adequate and well-controlled trials investigating congenital abnormalities. As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account. In the present case, the use in pregnant women of zidovudine, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV.

Zidovudine has been associated with reproductive toxicity findings in animal studies. Zidovudine may inhibit cellular DNA replication and has been shown to be transplacental carcinogen in one animal study. The clinical relevance of these findings is unknown. Zidovudine has been shown to cross the placenta in humans (see section 5.2). 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) such as RETROVIR IV. The clinical relevance of these elevations in serum lactate is unknown. There have also been reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and RETROVIR IV exposure in utero or peri-partum has not been established.

Lactation:

Women infected with HIV should not breastfeed 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 breastfeeding 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 fixed dose combination e.g. lamivudine/zidovudine) 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, RETROVIR IV has not been shown to affect sperm count, morphology or motility.

4.7 Effects on ability to drive and use machines:

There have been no studies to investigate the effect of RETROVIR IV on driving performance or the ability to operate machinery. RETROVIR IV causes dizziness and loss of mental activity that might interfere with ability to drive or operate machinery.

4.8 Undesirable effects:

The following events have been reported in patients treated with RETROVIR IV.

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 transfusion), neutropenia and leucopenia. Dosage reduction or cessation of therapy may become necessary (see section 4.2). The incidence of neutropenia was also increased in patients with pre-existing neutropenia or anaemia and those with low vitamin B_{12} levels.

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), anorexia

Treatment with RETROVIR IV has been associated with loss of subcutaneous fat (see section 4.4).

Psychiatric disorders

Rare: anxiety and depression

Nervous system disorders

Very common: headache

Common: dizziness

Rare: insomnia, paraesthesiae, 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 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 infrequency

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.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of RETROVIR IV is important. It allows continued monitoring of the benefit/risk balance of RETROVIR IV. Health care providers are asked to report any suspected adverse reactions to: SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms and signs:

No specific symptoms or signs have been identified following acute overdose with RETROVIR IV apart from those listed as undesirable effects (see section 4.8).

Treatment:

Patients should be observed closely for evidence of toxicity (see section 4.8) and given the necessary supportive therapy. Haemodialysis and peritoneal dialysis, appears to have a limited effect on elimination of zidovudine but enhances the elimination of the glucuronide metabolite.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: nucleoside analogue, ACT code: J05A F01

Zidovudine is a nucleoside reverse-transcriptase inhibitor (NRTI). Zidovudine is an antiviral medicine which is active *in vitro* against retroviruses including the Human Immunodeficiency Virus (HIV, also known as HTLV-III or LAV). The HIV infection is unlikely to be completely eradicated by zidovudine treatment because the viral genome is integrated into the host DNA. 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 and then the triphosphate (TP) derivative is catalysed by cellular thymidylate kinase and nonspecific 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. No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

RETROVIR in combination with other ARVs

Resistance to zidovudine develops *in vitro* and *in vivo* with zidovudine monotherapy.

In combination studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delaviridine or interferon-alpha, zidovudine showed additive or synergistic activity in cell culture. The relationship between the *in vitro* susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Studies *in vitro* of zidovudine in combination with lamivudine indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Furthermore *in vivo* there is clinical evidence that zidovudine plus lamivudine delays the emergence of zidovudine resistance in anti-retroviral naïve patients.

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.

5.2 Pharmacokinetic properties:

Dose independent kinetics were observed in adult patients receiving one-hour infusions of 1 to 5 mg/kg three to six times daily. Total body clearance was 1 900 mL/min/kg and the terminal plasma half-life was approximately 1,1 hours. 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 and accounts for about 50-80 % of the dose eliminated by renal excretion. No other metabolites have been observed. Mean steady state peak (Css_{max}) and trough (Css_{min}) plasma concentrations in adults following a one-hour infusion of 2,5 mg/kg every 4 hours were 4,0 and 0,4 µM respectively (or 1,1 and 0,1 µg/mL). Plasma protein binding is relatively low (34 to 38 %) and so medicine interactions involving binding site displacement are not anticipated. In adults the average cerebrospinal fluid/plasma zidovudine concentration ratio 2 to 4 hours after chronic intermittent oral dosing was found to be approximately 0,5. Limited data indicate that zidovudine crosses the placenta and is found in amniotic fluid and foetal blood. In children over the age of five months, the pharmacokinetic profile of zidovudine is similar to that in adults. During continuous intravenous infusion in children, the mean steady-state cerebrospinal fluid/plasma concentration ratio was 0,24. The limited 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.

Pharmacokinetics in pregnancy:

The pharmacokinetics of zidovudine in eight women during the last trimester of pregnancy were 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. The elimination half-life in newborn infants was 13,8 hours.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Hydrochloric acid, sodium hydroxide, water for injection.

6.2 Incompatibilities:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life:

36 months.

Refer to section 6.6 for shelf life after opening.

6.4 Special precautions for storage:

Store at or below 30 °C.

Protect from light.

6.5 Nature and contents of container:

An amber glass vial, sealed with a rubber stopper and aluminium collar with plastic flip-top cover, containing 200 mg zidovudine in 20 mL.

6.6 Special precautions for disposal and other handling:

The required dose should be added to and mixed with glucose intravenous infusion BP (5 % *m/v*) to give a final zidovudine concentration of either 2 mg or 4 mg/mL. These dilutions are chemically and physically stable for up to 48 hours at both 5 °C and 25 °C.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

29/20.2.8/0483

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