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CLEAN PROPOSED PROFESSIONAL INFORMATION APRIL 2026

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DIZOVIN 100 CAPSULES

DIZOVIN 300 TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DIZOVIN 100 CAPSULES

Each capsule contains zidovudine 100 mg.

DIZOVIN 300 TABLETS

Each tablet contains zidovudine 300 mg.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DIZOVIN 100 CAPSULES

White to off-white opaque, size 3 capsules, containing white to off-white powder with 'ML 21' on cap and '100' on body imprinted with black ink.

DIZOVIN 300 TABLETS

White, circular, biconvex, film coated tablets having 'ML8' debossed on the periphery of one side and plain surface on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIZOVIN is indicated in combination with other antiretroviral medicines for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children over the age of 12 years**.**

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DIZOVIN is also indicated for the management of patients with advanced HIV disease, such as those with Acquired Immune Deficiency Syndrome (AIDS) or AIDS-Related Complex (ARC). It is shown that in children with symptomatic HIV infection and markers indicative of significant immune suppression are consistent with experience in adults.

DIZOVIN is indicated in pregnancy to reduce the rate of maternal-foetal transmission of HIV. However, infants of these mothers should not be breastfed.

4.2 Posology and method of administration

Posology

Dosage in adults and children over the age of 12 years:

The recommended dose of DIZOVIN in combination with other antiretroviral medicines in adults and children over the age of 12 years is 500 or 600 mg/day in two or three divided doses. For dosages of antiretroviral medicines used in combination therapy in advanced HIV infection please consult the Professional Information of the individual medicines.

Dosage in the prevention of maternal-foetal transmission:

Pregnant women (over 14 weeks of gestation) should be given 500 mg/day orally, in divided doses until the beginning of labour. The newborn infants should be given 2 mg/kg body mass orally every 6 hours starting within 12 hours after birth and continuing until 6 weeks old. Infants unable to receive oral dosing should be given an intravenous zidovudine formulation at 1,5 mg/kg body mass infused over 30 minutes every 6 hours.

***Dosage adjustments in patients with haematological toxicity*:**

Dosage reduction or interruption of **DIZOVIN** 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 adjustments in recipients of a combination of DIZOVIN and other antiretroviral therapy:

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For recipients of a combination of DIZOVIN and other antiretroviral therapy, dosage adjustments for either medicine should follow the guidelines for the individual medicine. For severe adverse events, those in which the causative medicine is unclear or those persisting after dose interruption or reduction of one medicine, the other medicine should also be interrupted or dose reduced. Medical practitioners should refer to the complete product information for the other antiretroviral medicines for a description of known adverse reactions.

Special populations

***Dosage in the elderly*:**

DIZOVIN 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 the decrease in renal function and alterations in haematological parameters. Appropriate monitoring of patients before and during use of **DIZOVIN** is advised.

***Dosage in renal impairment*:**

Compared to healthy subjects, patients with advanced renal failure have a 50 % higher maximum plasma concentration of **DIZOVIN**. 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

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

Method of administration

Oral use

4.3 Contraindications

DIZOVIN is contra-indicated in patients known to be hypersensitive to zidovudine or to any of the ingredients of **DIZOVIN,** see in section 6.

DIZOVIN is contra-indicated in patients who have had potentially life-threatening allergic reactions, e.g. anaphylaxis, Stevens-Johnson syndrome to any of the components of **DIZOVIN**.

DIZOVIN 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/decilitre).

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

Children < 3 months: The limited data available are insufficient to propose specific dosage recommendations.

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4.4 Special warnings and special precautions for use

DIZOVIN has been associated with haematologic toxicity including neutropenia and severe anaemia, particularly in patients with advanced HIV-1 disease.

Prolonged use of DIZOVIN has been associated with symptomatic myopathy.

Lactic acidosis and severe hepatomegaly with steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been

reported with use of lamivudine alone or in combination, in the treatment of HIV infection. A majority of these cases were 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).

Haematological:

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 **DIZOVIN**. These occurred more frequently at higher dosages (1200 – 1500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease. Therefore haematological parameters should be carefully monitored. For patients with advanced symptomatic HIV disease it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter. In patients with early HIV disease (where bone marrow reserve is generally good), haematological toxicity is less frequent. Depending on the overall condition of the patient, blood tests may be performed less often, for example every one to three months. If the haemoglobin level falls to between 7,5 g/dl (4,65 mmol/l) and 9 g/dl (5,59 mmol/l) or the neutrophil count falls to between 0,75 x 10^9/l and 1,0 x 10^9/l, the daily dosage may be reduced until there is

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evidence of marrow recovery, alternatively, recovery may be enhanced by brief (2 - 4 weeks) interruption of **DIZOVIN** therapy. Marrow recovery is usually observed within 2 weeks after which time **DIZOVIN** therapy at a reduced dosage may be reinstituted. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (see section 4.1).

Lactic Acidosis/hyperlactataemia:

Use of **DIZOVIN** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

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 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 **DIZOVIN** to patients with known factors for liver disease.

Treatment with **DIZOVIN** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatoxicity.

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

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dysfunction in HIV-negative infants exposed *in utero* and/or post-natally 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 signs or symptoms.

Pancreatitis:

Pancreatitis has been observed in some patients receiving **DIZOVIN**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **DIZOVIN** 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 **DIZOVIN** is increased due to decreased clearance. The dose of **DIZOVIN** should therefore be adjusted (see section 4.2).

Liver disease:

Use of **DIZOVIN** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **DIZOVIN** 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 professional information 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.

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Patients with HIV and hepatitis B or C virus co-infection:

Patients with chronic hepatitis B or C and treated with antiretroviral 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 Professional Information for these medicines.

Patients co-infected with HIV and HBV who discontinue **DIZOVIN** 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.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically it presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the

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opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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 **DIZOVIN** 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:

Patients should be advised that current antiretroviral therapy, including **DIZOVIN**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Prevention of maternal-foetal transmission:

Haemoglobin concentrations in infants exposed to **DIZOVIN** 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 **DIZOVIN** therapy. The long-term consequences of *in utero* and infant exposure to **DIZOVIN** are unknown.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially

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"sodium-free".

4.5 Interactions with other medicines and other forms of interaction

DIZOVIN 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 **DIZOVIN**. The interactions listed below should not be considered exhaustive but are representative of the classes of medicines where caution should be exercised.

Patients should be cautioned about the concomitant use of self- administered medicines. Phenytoin blood levels have been reported to be low in some patients receiving **DIZOVIN**, while in some patients a high level is noted. These observations suggest that phenytoin levels should be carefully monitored in patients receiving both medicines.

Other medicines (such as aspirin, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine) may also alter the metabolism of **DIZOVIN** by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of interactions before using such medicines (particularly those impairing glucuronidation or directly inhibiting hepatic microsomal metabolism) especially in chronic therapy in combination. Concomitant therapy with potentially nephrotoxic or myelosuppressive medicines (e.g. dapsone, systemic pentamidine, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon alfa, vincristine, vinblastine and doxorubicin) may also increase the haematological toxicity with **DIZOVIN**. 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 both medicines should be reduced. **DIZOVIN** in combination with either ribavirin, doxorubicin or stavudine is antagonistic *in vitro*. The concomitant use of either of these medicines with **DIZOVIN** should be avoided.

Since some patients receiving **DIZOVIN** may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Limited data do not indicate an increased risk of toxicity with co-trimoxazole, aerosolised pentamidine,

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pyrimethamine and acyclovir. Limited data suggest that probenecid increases the mean half-life and area under the plasma concentration curve of zidovudine, by decreasing glucuronidation. Renal excretion of glucuronide (and possibly **DIZOVIN** itself) is reduced in the presence of probenecid.

Limited data suggests that co-administration of **DIZOVIN** and rifampicin decreases the AUC of zidovudine by 48 % ± 34 %. However, the clinical significance of this is unknown.

A modest increase in C_{max} (28 %) is observed for **DIZOVIN** when administered with lamivudine, however overall exposure (AUC) is not significantly altered. **DIZOVIN** has no effect on the pharmacokinetics of lamivudine.

Decreased zidovudine clearance and increased area under the zidovudine plasma concentration-time curve has been seen in patients receiving methadone. Patients should be monitored for increased incidence of nausea and vomiting.

Studies have indicated that absorption of zidovudine is reduced by clarithromycin. **DIZOVIN** and clarithromycin should be given at least two hours apart since this has shown to have no overall effect on the bioavailability of **DIZOVIN**.

Valproate has been shown to increase the plasma concentration of zidovudine and the area under the zidovudine plasma concentration-time curve due to reduced glucuronidation of zidovudine.

Pharmacokinetics of zidovudine when used in combination with other antiretroviral medicines:

Co-administration of lamivudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

There were no clinically significant alterations to zidovudine pharmacokinetics when given concomitantly with the following antiretroviral medicines: Nucleoside reverse transcriptase inhibitors (NRTI's): zalcitabine didanosine and abacavir; non-nucleoside reverse transcriptase inhibitors (NNRTI's): nevirapine and efavirenz, and protease inhibitors: indinavir sulphate, saquinavir mesylate, ritonavir amprenavir and nelfinavir.

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Zidovudine administration does not result in any clinically significant alterations to the pharmacokinetics of the above listed medicines when given concomitantly.

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

Administration of co-trimoxazole with the **DIZOVIN**/lamivudine combination in patients with renal impairment should be carefully assessed.

4.6 Fertility, pregnancy and lactation

Pregnancy

DIZOVIN can be given to pregnant women over 14 weeks of gestation until the beginning of labour (see section 4.2).

Pregnant women considering the use of **DIZOVIN** during pregnancy for prevention of HIV transmission to their infants should be advised that the transmission may still occur despite therapy. It is therefore recommended that mothers taking **DIZOVIN** do not breastfeed their infants. The safety of **DIZOVIN** for the mother and foetus during the first trimester of pregnancy has not been established.

Breastfeeding

DIZOVIN is excreted in human milk.

The mean concentration of zidovudine is similar in human milk and serum. Therefore, as zidovudine and the virus pass into breast milk it is recommended that mothers taking **DIZOVIN** do not breastfeed their infants.

Mothers should therefore be instructed to discontinue breastfeeding if they are receiving **DIZOVIN**, because of the potential for adverse reaction from zidovudine in breastfed infants. Women infected with HIV should not breastfeed their infants in order to avoid the transmission of HIV.

4.7 Effects on ability to drive and use machines

DIZOVIN may cause dizziness, impaired concentration and/or drowsiness. Patients should be

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instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequent	anaemia, granulocytopenia, lymphadenopathy, neutropenia, thrombocytopenia.
	Frequency unknow	aplastic anaemia, haemolytic anaemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia.
Immune system disorder	Frequency unknown	sensitisation reactions including anaphylaxis and angioedema.
Endocrine disorders	Frequency unknown	Gynaecomastia
Metabolism and nutrition disorders	Frequent	Lactic acidosis (see section 4.4)
	Frequency unknown	redistribution/accumulation of body fat.
Psychiatric disorders	Frequency unknown	anxiety, confusion, depression, loss of mental acuity, mania
Nervous system disorders	Frequent	Headache, malaise, chills, fatigue, insomnia, fever
	Frequency unknown	dizziness, paraesthesia, seizures, somnolence, vertigo.
Eye disorders	Frequency	macular oedema, photophobia.

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	unknown	
Ear and labyrinth disorders	Frequent	pain, discharge, erythema or swelling of the ear.
	Frequency unknown	hearing loss, amblyopia
Cardiac disorders	Frequency unknown	Cardiomyopathy, syncope
Vascular disorders	Frequency unknown	vasculitis
Respiratory, thoracic and mediastinal disorders	Frequent	cough, abnormal breath sounds/wheezing.
	Frequency unknown	rhinitis, sinusitis.
Gastrointestinal disorders	Frequent	constipation, abdominal cramps, abdominal pain, dyspepsia, diarrhoea, stomatitis.
	Less frequent	anorexia, nausea, vomiting.
	Frequency unknown	dysphagia, flatulence, oral mucosa pigmentation, mouth ulcers
Hepato-biliary disorders	Less Frequent	hyperbilirubinaemia, hepatomegaly.
	Frequency unknown	hepatitis, hepatomegaly with steatosis, jaundice, pancreatitis.
Skin and subcutaneous disorders	Frequent	Rash
	Frequency unknown	changes in skin and nail pigmentation, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, increased sweating, urticaria.

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Musculoskeletal, connective tissue and bone disorders	Frequent	asthenia, arthralgia, musculoskeletal pain, myalgia, neuropathy
	Frequency unknown	muscle spasm, myopathy and myositis with pathological changes, rhabdomyolisis, tremor.
Renal and Urinary disorders	Frequency unknown	urinary frequency, urinary hesitancy
General disorders	Frequency unknown	back pain, chest pain, flu-like syndrome, generalised pain.
Investigations	Frequent	ALT >10 ULN; AST >10 ULN; lipase > 2.5 x ULN; total amylase > 2.5 x ULN.
	Frequency unknown	increased CPK, increased LDH.

Reporting of suspected adverse reactions

If you get side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com By reporting side effects, you can help provide more information on the safety of **DIZOVIN.**

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4.9 Overdose

No specific symptoms or signs have been identified following acute overdose with **DIZOVIN** apart from those listed as side effects such as fatigue, headache, vomiting, and occasional reports of haematological disturbances. Patients should be observed closely for evidence of toxicity (see see section 4.8) and given the necessary supportive therapy. Haemodialysis appears to have a limited effect on elimination of zidovudine but enhances the elimination of the glucuronide metabolite.

5. PHARMACOLOGICAL ACTION PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antiviral agents

Zidovudine, a thymidine nucleoside analogue, is an antiviral agent 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 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.

Zidovudine in combination with other antiretroviral therapy:

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

Zidovudine has been shown to act additively or synergistically with a number of anti-HIV agents. Inhibiting the replication of HIV in cell culture. In combination studies with didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delavirdine, zalcitabine or interferon-alpha, zidovudine showed additive or synergistic activity in cell culture. The relationship

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between the *in vitro* susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine. Furthermore, *in vivo*, there is evidence showing that zidovudine plus lamivudine delays the emergence of zidovudine-resistant isolates in individuals with no prior antiretroviral therapy.

5.2 Pharmacokinetic properties

Adults:

Zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0,5 to 1,5 hours after oral administration. The apparent volume of distribution of zidovudine, following oral administration, is 1,6 ± 0,6 L/kg and binding to plasma protein is low, < 38 %.

Zidovudine is primarily eliminated by hepatic metabolism. T_{max} is approximately 1,1 hours. Renal clearance 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 administered dose eliminated by renal excretion. 3'amino-3'-deoxythymidine has been identified as a metabolite of zidovudine. Pharmacokinetics of zidovudine is dose independent at oral dosing regimes ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

Special populations:

Renal and hepatic impairment:

There are limited data concerning the pharmacokinetics of zidovudine in patients with renal or hepatic impairment. No data are available on the pharmacokinetics of zidovudine in the elderly.

Dialysis:

In patients on chronic dialysis, doses of 300 mg/day in divided dosages resulted in plasma levels similar to those of normal volunteers on 500-600 mg/day.

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Children:

Zidovudine clearance is significantly reduced in children less than one month of age.

In children over the age of five months, the pharmacokinetic profile of zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and at all dose levels the bioavailability is 60-74 % with a mean of 65 %. The mean terminal plasma half-life and total body clearance are 1,5 hours and 30,9 ml/min/kg respectively. The major metabolite is the 5'-glucuronide. 29 % of the dose is 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 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 during the last trimester of pregnancy are similar to that of non-pregnant women. Consistent with passive transmission of the medicine across the placenta, zidovudine concentrations in infant plasma at birth are essentially equal to those in maternal plasma at delivery. The elimination half-life in newborn infants is 13,8 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DIZOVIN 100 CAPSULES

microcrystalline cellulose, corn starch, sodium starch glycolate, magnesium stearate, hard gelatin capsules size 3: titanium dioxide, gelatin, sodium lauryl sulfate.

DIZOVIN 300 TABLETS

microcrystalline cellulose, sodium starch glycolate, povidone K 29/32, magnesium stearate, colourant: opadry white 03B28796.

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6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ˚C.

The HDPE containers must be kept tightly closed.

6.5 Nature and contents of container

DIZOVIN 100 CAPSULES

Round, white HDPE containers with 100 capsules.

DIZOVIN 300 TABLETS

Round, white HDPE containers with 56 or 60 tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

Tel 011 682 1169

8. REGISTRATION NUMBER:

DIZOVIN 100: 45/20.2.8/0085

DIZOVIN 300: 45/20.2.8/0086

VR

Type IA_{IN} – C.I.0.1: Format update in accordance with relevant changes to the Act, general regulations and guidelines
Type IA_{IN} – C.I.0.2.a: Editorial changes to align with changes to the Act, general regulations and guidelines

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 07 December 2012

10. DATE OF REVISION OF THE TEXT

TBC

VR

Type IA_{IN} – C.I.0.1: Format update in accordance with relevant changes to the Act, general regulations and guidelines
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