1.6 Product Information

1.6.1 Summary of Product Characteristics (SmPC)

Summary of Product Characteristics (SmPC) for **Zidovudine Oral Solution USP 50 mg/5ml** is enclosed overleaf.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Zidovudine oral solution USP 50mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral solution contains Zidovudine USP 50 mg

Excipients: Sucrose, glycerin, citric acid, sodium benzoate, strawberry flavor and purified water**.**

PHARMACEUTICAL FORM: Colorless to pale yellow strawberry flavoured syrup. Zidovudine oral solution available in bottles of 240 ml. An oral dosing syringe along with adapter is included in the pack.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zidovudine oral solution is indicated in anti-retroviral combination therapy for Human Immunodeficiency Virus (HIV) infected adults and children.

Zidovudine oral solution chemoprophylaxis is indicated for use in HIV-positive pregnant women (over 14 weeks of gestation) for prevention of maternal-foetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants.

4.2 Posology and method of administration

Dosage in adults:

The usual recommended dose of zidovudine oral solution in combination with other anti-retroviral agents is 500 or 600 mg/day in two or three divided dose.

Dosage in children:

3 months - 12 years:

The recommended dose of zidovudine oral solution is 360 to 480 mg/m^2 per day, in 3 or 4 divided doses in combination with other antiretroviral agents. The maximum dosage should not exceed 200 mg every 6 hours.

<3 months:

The limited data available are insufficient to propose specific dosage recommendations (See below -maternal foetal transmission and 5.2 Pharmacokinetic properties).

Dosage in the prevention of maternal-foetal transmission:

Although the optimal dosage schedule has not been identified 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 per day) until the beginning of labour. During labour and delivery zidovudine should be administered intravenously at 2 mg/kg bodyweight given over one 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 orally every 6 hours starting within 12 hours after birth and continuing until 6 weeks old (e.g. a 3 kg neonate would require a 0.6 ml dose of oral solution every 6 hours).

Due to the small volumes of oral solution required, care should be taken when calculating neonate doses. To facilitate dosing precision a 1 ml syringe is included in the neonate pack.

Infants unable to receive oral dosing should be given zidovudine intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours. In case of planned caesarean, the infusion should be started 4 hours before the operation. In the event of a false labour, the zidovudine infusion should be stopped and oral dosing restarted.

Dosage adjustments in patients with haematological adverse reactions:

Dosage reduction or interruption of zidovudine oral soloution 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 4.3 Contraindications and 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 zidovudine oral solution is advised.

Dosage in renal impairment:

In patients with severe renal impairment, apparent zidovudine clearance after oral zidovudine administration was approximately 50% of that reported in healthy subjects with normal renal function. Therefore a dosage reduction to 300-400mg daily is recommended for patients with severe renal impairment with creatinine clearance -≤ 10ml/min. 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.

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 reductions 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, such as the development of haematological adverse reactions (anaemia, leucopenia, neutropenia) and reduce the dose and/or increase the interval between doses as appropriate.

4.3 Contraindications:

Zidovudine oral solution is contra-indicated in patients known to be hypersensitive to zidovudine, or to any of the components of the formulations.

Zidovudine oral solution should not be given to patients with abnormally low neutrophil counts (less than 0.75 x 10^9/litre) or abnormally low haemoglobin levels (less than 7.5 g/decilitre or 4.65 mmol/litre).

Zidovudine oral solution is contra-indicated in new born infants with hyperbilirubinaemia requiring treatment other than phototherapy, or with increased transaminase levels of over five times the upper limit of normal.

4.4 Special warnings and precautions for use

Zidovudine oral solution 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.

Zidovudine oral solution should be administered under the supervision of a doctor with experience of treating patients with HIV infection or AIDS. An appropriate treatment procedure requires access to suitable facilities eg. for performing haematological monitoring investigations, including determination of viral load, CD4 lymphocytes and for provision of blood transfusions if necessary.

The concomitant use of rifampicin, ribavirin or stavudine with zidovudine should be avoided (see section 4.5 Interactions with other Medicaments and other forms of Interaction).

Haematological Adverse Reactions: Anaemia (usually not observed before six weeks of zidovudine oral solution 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 receiving zidovudine oral solution; These occurred more frequently at higher dosages (1200-1500mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease.

Haematological parameters should be carefully monitored. For patients with advanced symptomatic HIV disease it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter. In patients with early HIV disease (where bone marrow reserve is generally good), haematological adverse reactions are infrequent. Depending on the overall condition of the patient, blood tests may be performed less often, for example every 1 to 3 months.

If the haemoglobin level falls to between 7.5 g/dl (4.65 mmol/l) and 9 g/dl (5.59 mmol/l) or the neutrophil count falls to between 0.75 x 10^9/l and 1.0 x 10^9/l, the daily dosage may be reduced until there is evidence of marrow recovery; alternatively,

recovery may be enhanced by brief (2-4 weeks) interruption of zidovudine oral solution therapy. Marrow recovery is usually observed within 2 weeks after which time zidovudine oral solution therapy at a reduced dosage may be reinstituted. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (see 4.3 Contra-indications).

*Lactic acidosis:*Lactic acidosis usually associated with hepatomegaly and hepatic steatosis has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels. Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Mitochondrial toxicity: 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 post-natally to nucleoside analogues. The main adverse events reported are haematological disorders (anemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently

unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8 Undesirable effects).

Liver disease: The safety and efficacy of zidovudine has not been established in patients with significant underlying liver disorders.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please also refer to the relevant product information for these medicinal products.

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 according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered (see section 4.2).

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

Patients should be advised that zidovudine oral solution therapy has not been proven to prevent the transmission of HIV to others through sexual contact or blood contamination.

Use in Elderly and in Patients with Renal or Hepatic Impairment: See 4.2 Posology and method of administration.

4.5 Interaction with other medicinal products and other forms of interaction :

Limited data suggests that co-administration of zidovudine with rifampicin decreases the AUC (area under the plasma concentration curve) of zidovudine by 48% ± 34%. This may result in a partial loss or total loss of efficacy of zidovudine (see 4.4 Special warnings and precautions for use).

Zidovudine in combination with either ribavirin or stavudine are antagonistic in vitro. The concomitant use of either ribavirin or stavudine with zidovudine should be avoided (see 4.4 Special warnings and precautions for use).

Probenecid increases the AUC of zidovudine by 106% (range 100 to 170%). Patients receiving both drugs should be closely monitored for haematological toxicity.

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 blood levels have been reported to be low in some patients receiving zidovudine oral solution, while in one patient a high level was noted. These observations suggest that phenytoin levels should be carefully monitored in patients receiving both drugs.

In a pharmacokinetic study co-administration of zidovudine and atovaquone showed a decrease in zidovudine clearance after oral dosing leading to a 35%±23% increase in plasma zidovudine AUC. Given the limited data available the clinical significance of this is unknown.

Valproic acid, fluconazole or methadone when co-administered with zidovudine have been shown to increase the AUC with a corresponding decrease in its clearance. As only limited data are available the clinical significance of these findings is unclear but if zidovudine is used concurrently with either valproic acid, fluconazole or methadone, patients should be monitored closely for potential toxicity of zidovudine .

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive drugs (eg. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine . If concomitant therapy with any of these drugs 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 zidovudine may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such prophylaxis has included co-trimoxazole, aerosolised pentamidine, pyrimethamine and aciclovir. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these drugs at doses used in prophylaxis. Clarithromycin tablets reduce the absorption of zidovudine.

4.6 Pregnancy and lactation

Pregnancy:

The use of zidovudine oral solution 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 based on viral cultures in infants.

The results from the pivotal U.S. placebo-controlled study indicated that zidovudine reduced maternal-foetal transmission by approximately 70%. In this study, pregnant women had CD4 cell counts of 200 to 1818/mm^3 (median in treated group 560/ mm^3) and began treatment therapy between weeks 14 and 34 of gestation and had no clinical indications for zidovudine therapy; their newborn infants received zidovudine until 6-weeks old.

A decision to reduce the risk of maternal transmission of HIV should be based on the balance of potential benefits and potential risk. Pregnant women considering the use of zidovudine oral solution during pregnancy for prevention of HIV transmission to their infants should be advised that transmission may still occur in some cases despite therapy.

The efficacy of zidovudine to reduce the maternal-foetal transmission in women with previously prolonged treatment with zidovudine or other antiretroviral agents or women infected with HIV strains with reduced sensitivity to zidovudine is unknown.
It is unknown whether there are any long-term consequences of in utero and infant exposure to zidovudine.
Based on the animal carcinogenicity / mutagenicity findings a carcinogenic risk to humans cannot be excluded (See 5.3 Preclinical safety data). The relevance of these findings to both infected and uninfected infants exposed to zidovudine is unknown. However, pregnant women considering using zidovudine oral solution during pregnancy should be made aware of these findings.
Given the limited data on the general use of zidovudine oral solution in pregnancy, zidovudine oral solution should only be used prior to the 14th week of gestation when the potential benefit to the mother and foetus outweigh the risks. Studies in pregnant rats and rabbits given zidovudine orally at dosage levels up to 450 and 500 mg/kg/day respectively during the major period of organogenesis have revealed no evidence of teratogenicity. There was, however, a statistically significant increase in foetal resorptions in rats given 150 to 450 mg/kg/day and in rabbits given 500 mg/kg/day.
A separate study, reported subsequently, found that rats given a dosage of 3000 mg/kg/day, which is very near the oral median lethal dose (3683 mg/kg), caused marked maternal toxicity and an increase in the incidence of foetal malformations. No evidence of teratogenicity was observed in this study at the lower dosages tested (600 mg/kg/day or less).

Fertility:

Zidovudine did not impair male or female fertility in rats given oral doses of up to 450 mg/kg/day. There are no data on the effect of zidovudine oral solution on human female fertility. In men, zidovudine oral solution have not been shown to affect sperm count, morphology or motility.

Lactation:

Health experts recommend that women infected with HIV do not breast feed their infants in order to avoid the transmission of HIV. After administration of a single dose of 200 mg zidovudine to HIV-infected women, the mean concentration of

zidovudine was similar in human milk and serum. Therefore, since the drug and the virus pass into breast milk it is recommended that mothers taking zidovudine oral solution do not breast feed their infants.

Effects on ability to drive and use machines:

There have been no studies to investigate the effect of zidovudine oral solution on driving performance or the ability to operate machinery. Furthermore, a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless, the clinical status of the patient and the adverse event profile of zidovudine oral solution should be borne in mind when considering the patient's ability to drive or operate machinery.

Undesirable effects:

The adverse event profile appears similar for adults and children. The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia. These occurred more frequently at higher dosages (1200-1500mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts less than $100/mm^3$. Dosage reduction or cessation of therapy may become necessary (see 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 zidovudine oral solution therapy.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (See 4.4 Special Warnings and Precautions for Use).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance,

hyperglycaemia and hyperlactataemia (see section 4.4 Special warnings and special precautions for use).

The following events have been reported in patients treated with zidovudine oral solution. They may also occur as part of the underlying disease process or in association with other drugs used in the management of HIV disease. The relationship between these events and use of zidovudine oral solution is therefore difficult to evaluate, particularly in the medically complicated situations which characterise advanced HIV disease. A reduction in dose or suspension of zidovudine oral solution therapy may be warranted in the management of these conditions.

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as Very common (greater than 10%), Common (1 - 10%), Uncommon (0.1-1%), Rare (0.01-0.1%) and Very rare (less than 0.01%).

Blood and lymphatic system disorders

Common: Anaemia, neutropenia and leucopenia.

Uncommon: Thrombocytopenia and pancytopenia with marrow hypoplasia

Rare: Pure red cell aplasia

Very rare: Aplastic anaemia

Metabolism and nutrition disorders

Rare: Anorexia and lactic acidosis in the absence of hypoxaemia

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 pruritis

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 disorders :

Common: Malaise

Uncommon: Fever, generalised pain and asthenia

Rare: Chills, chest pain and influenza-like syndrome

The available data from both placebo-controlled and open-label studies indicate that the incidence of nausea and other frequently reported clinical adverse events consistently decreases over time during the first few weeks of therapy with zidovudine.

Adverse reactions with zidovudine oral solution for the prevention of maternal-foetal transmission:

In a placebo-controlled trial, overall clinical adverse events and laboratory test abnormalities were similar for women in the zidovudine and placebo groups.

However, there was a trend for mild and moderate anaemia to be seen more commonly prior to delivery in the zidovudine treated women.

In the same trial, haemoglobin concentrations in infants exposed to zidovudine oral solution for this indication were marginally lower than in infants in the placebo group, but transfusion was not required. Anaemia resolved within 6 weeks after completion of zidovudine oral solution therapy. Other clinical adverse events and laboratory test abnormalities were similar in the zidovudine oral solution and placebo groups. It is unknown whether there are any long-term consequences of *in utero* and infant exposure to zidovudine oral solution.

Overdose

Symptoms and signs:

No specific symptoms or signs have been identified following acute overdose with zidovudine apart from those listed as undesirable effects such as fatigue, headache, vomiting, and occasional reports of haematological disturbances. Following a report where a patient took an unspecified quantity of zidovudine with serum levels consistent with an overdose of greater than 17 grams there were no short term clinical, biochemical or haematological sequelae identified.

Treatment:

Patients should be observed closely for evidence of toxicity (See 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group – nucleoside analogue – ATC Code J05A F01

Mode of action:

Zidovudine is an antiviral agent which is highly active *in vitro* against retroviruses including the Human Immunodeficiency Virus (HIV).

Zidovudine is phosphorylated in both infected and uninfected cells to the monophosphate (MP) derivative by cellular thymidine kinase. Subsequent

phosphorylation of zidovudine -MP to the diphosphate (DP), and then the triphosphate (TP) derivative is catalysed by cellular thymidylate kinase and non-specific kinases respectively. Zidovudine -TP acts as an inhibitor of and substrate for the viral reverse transcriptase. The formation of further proviral DNA is blocked by incorporation of zidovudine -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.

Clinical virology:

The relationships between *in vitro* susceptibility of HIV to zidovudine and clinical response to therapy remain under investigation. *In vitro* sensitivity testing has not been standardized and results may therefore vary according to methodological factors. Reduced *in vitro* sensitivity to zidovudine has been reported for HIV isolates from patients who have received prolonged courses of zidovudine therapy. The available information indicates that for early HIV disease, the frequency and degree of reduction of *in vitro* sensitivity is notably less than for advanced disease.

The reduction of sensitivity with the emergence of zidovudine resistant strains limits the usefulness of zidovudine monotherapy clinically. In clinical studies, clinical end-point data indicate that zidovudine, particularly in combination with lamivudine, and also with didanosine or zalcitabine results in a significant reduction in the risk of disease progression and mortality. The use of a protease inhibitor in a combination of zidovudine and lamivudine has been shown to confer additional benefit in delaying disease progression, and improving survival compared to the double combination on its own.

The anti-viral effectiveness *in vitro* of combinations of anti-retroviral agents are being investigated. Clinical and *in vitro* studies of zidovudine in combination with lamivudine indicate that zidovudine -resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. Furthermore there is clinical evidence that zidovudine plus lamivudine delays the emergence of zidovudine resistance in anti-retroviral naive patients.

In some *in vitro* studies zidovudine has been shown to act additively or synergistically with a number of anti-HIV agents, such as lamivudine, didanosine,

and interferon-alpha, inhibiting the replication of HIV in cell culture. However, *in vitro* studies with triple combinations of nucleoside analogues or two nucleoside analogues and a protease inhibitor have been shown to be more effective in inhibiting HIV-1 induced cytopathic effects than one or two drug combinations.

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 involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to AZT as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

In the US ACTG076 trial, zidovudine was shown to be effective in reducing the rate of maternal-foetal transmission of HIV-1 (23% infection rate for placebo versus 8% for zidovudine) when administered (100 mg five times daily) to HIV-positive pregnant women (from week 14-34 of pregnancy) and their newborn infants (2mg/kg every 6 hours) until 6 weeks of age. In the shorter duration 1998 Thailand CDC study, use of oral zidovudine therapy only (300 mg twice daily), from week 36 of pregnancy until delivery, also reduced the rate of maternal-foetal transmission of HIV (19% infection rate for placebo versus 9% for zidovudine). These data, and data from a published study comparing zidovudine regimes to prevent maternal-foetal HIV transmission have shown that short maternal treatments (from week 36 of pregnancy) are less efficacious than longer maternal treatments (from week 14-34 of pregnancy) in the reduction of perinatal HIV transmission.

5.2 Pharmacokinetic properties

Pharmacokinetics in adults:

Zidovudine is well absorbed from the gut and, at all dose levels studied, the bioavailability was 60-70%. From a bioequivalence study, steady-state mean (CV%) C[ss]max, C[ss]min, and AUC[ss] values in 16 patients receiving zidovudine 300mg twice daily were 8.57 (54%) microM (2.29 μg/ml), 0.08 (96%) microM (0.02 μg/ml), and 8.39 (40%) h*microM (2.24 h*μg/ml), respectively.

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

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucoronidated metabolite. 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.

There are limited data on the pharmacokinetics of zidovudine in patients with renal or hepatic impairment (see 4.2 Posology and method of administration). No specific data are available on the pharmacokinetics of zidovudine in the elderly.

Pharmacokinetics in children:

In children over the age of 5-6 months, the pharmacokinetic profile of zidovudine is similar to that in adults. Zidovudine is well absorbed from the gut and, at all dose levels studied, its bioavailability was 60-74% with a mean of 65%. C^{ss}max levels were 4.45μM (1.19μg/ml) following a dose of 120mg zidovudine/m^2 body surface area and 7.7μM (2.06μg/ml) at 180mg/m^2 body surface area. Dosages of 180 mg/m^2 four times daily in children produced similar systemic exposure (24 hour AUC 40.0 hr μM or 10.7 hr μg/ml) as doses of 200 mg six times daily in adults (40.7 hr μM or 10.9 hr μg/ml). The major metabolite is 5'-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.

Pharmacokinetics in pregnancy:

The pharmacokinetics of zidovudine has been investigated in a study of eight women during the third trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine was similar to that of non-pregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery.

Distribution:

In adults, the average cerebrospinal fluid/plasma zidovudine concentration ratio 2 to 4 hours after dosing was found to be approximately 0.5. Data indicate that zidovudine crosses the placenta and is found in amniotic fluid and foetal blood. Zidovudine has also been detected in semen and milk.

In children the mean cerebrospinal fluid/plasma zidovudine concentration ratio ranged from 0.52-0.85, as determined during oral therapy 0.5 to 4 hours after dosing. Plasma protein binding is relatively low (34 to 38%) and drug interactions involving binding site displacement are not anticipated.

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 *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 zidovudine 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 are unknown.

Carcinogenicity:

In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. 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. There were no other drug-related tumours observed in either sex of either species.

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, glycerin, citric acid, sodium benzoate, strawberry flavor and purified water

6.2 Incompatibilities

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

6.3 Shelf-life

24 months

After first opening the container: 30 days

6.4 Special precautions for storage

Store below 30^{o}C. Keep the bottle tightly closed. Store the bottle in the original outer carton.

6.5 Nature and contents of container

White opaque high density polyethylene bottle, containing 240 ml of oral solution, with a plastic cap and polyethylene wad. An oral dosing syringe along with adapter is included in the pack.

6.6 Instructions for use and handling

No special requirements

7 MARKETING AUTHORIZATION HOLDER :

AUROBINDO

M/s Aurobindo Pharma Ltd.,
Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad-500 038,
INDIA.