

Public Assessment Report

Decentralised Procedure

Zidovudine 100mg capsules, hard

Zidovudine 250mg capsules, hard

(zidovudine)

UK/H/1086/01-02/DC

UK licence numbers: PL 20532/0100-0101

Aurobindo Pharma Limited

LAY SUMMARY

On 1st August 2008, the MHRA granted Aurobindo Pharma Limited Marketing Authorisations (licences) for the medicinal products Zidovudine 100mg and 250mg Capsules, hard (PL 20532/0100-0101, UK/H/1086/01-02/DC). These are prescription-only medicines (POM).

Zidovudine Capsules contain the active ingredient, zidovudine, which belongs to a group of medicines called antiretrovirals. It slows down the progression of human immunodeficiency virus (HIV) infection, which can lead to Acquired Immune Deficiency Syndrome (AIDS), in both adults and children.

Zidovudine is used in combination with other antiretrovirals, for the treatment of HIV infected adults and children. It is also used in HIV positive pregnant women for preventing the transmission of the virus from mother to child.

The test products were considered to be generic versions of the reference products Retrovir Capsules 100mg and 250mg (PL 00003/0239 & 0240, The Wellcome Foundation Limited) based on the data submitted by Aurobindo Pharma Limited.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Zidovudine 100mg and 250mg Capsules, hard outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information about Initial Procedure

Product Name	Zidovudine 100mg capsules, hard Zidovudine 250mg capsules, hard
Type of Application	Generic, Article 10.1
Active Substance	Zidovudine
Form	Capsules, hard
Strength	100mg and 250mg
MA Holder	Aurobindo Pharma Limited, Ares, Odyssey Business Park, West End Road, South Ruislip HA4 6QD, United Kingdom.
Reference Member State (RMS)	UK
Concerned Member State (CMS)	Belgium, Germany, Spain, France
Procedure Number	UK/H/1086/01-02/DC
Timetable	Day 210 – 16 th July 2008

Module 2

Summary of Product Characteristics

Zidovudine 100mg capsules, hard

1 NAME OF THE MEDICINAL PRODUCT

Zidovudine 100 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of zidovudine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

White/white size '3' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'D' on white cap and '01' on white body with black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Zidovudine 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

Oral use.

Zidovudine should be prescribed by physicians who are experienced in the treatment of HIV infection.

Dosage in adults:

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

Dosage in children:

3 months - 12 years:

The recommended dose of Zidovudine is 360 to 480 mg/m² 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.

Less than 3 months:

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

Dosage in the prevention of maternal-foetal transmission:

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 one hour followed by a continuous intravenous infusion at 1 mg/kg/h until 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). Infants unable to receive oral dosing should be given zidovudine intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours.

If a caesarean childbirth is planned then an intravenous form of zidovudine should be started 4 hours before the operation.

In the event of a false labour, then the zidovudine infusion should be stopped and oral dosing restarted.

Refer to local, official guidelines for administration of zidovudine to neonates born to HIV-positive women.

Dosage adjustments in patients with haematological adverse reactions:

Substitution of zidovudine should be considered in patients whose haemoglobin level or neutrophil count fall to clinically significant levels. Other potential causes of anaemia or neutropenia should be excluded. Dose reduction or interruption of Zidovudine should be considered in the absence of alternative treatments (see sections 4.3 and 4.4).

Dosage in the elderly:

Zidovudine pharmacokinetics has 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 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 300-400 mg 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. For patients with end-stage renal disease maintained on haemodialysis or peritoneal dialysis, the recommended dose is 100 mg every 6-8 hours (300 mg – 400 mg daily)

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, due to the large variability in zidovudine exposures in patients with moderate to severe liver disease, 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 (see section 4.4).

4.3 Contraindications

- Hypersensitivity to zidovudine or to any of the excipients.
- Zidovudine should not be given to patients with abnormally low neutrophil counts (less than 0.75×10^9 /litre) or abnormally low haemoglobin levels (less than 7.5 g/decilitre or 4.65 mmol/litre).
- Zidovudine is contra-indicated in newborn 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 is not a cure for HIV infection or AIDS. Patients receiving Zidovudine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection.

The concomitant use of rifampicin or stavudine with zidovudine should be avoided (see section 4.5).

Haematological adverse reactions: Anaemia (usually not observed before six weeks of Zidovudine 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. 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 (see section 4.8).

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. 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 $0.75 \times 10^9/l$ and $1.0 \times 10^9/l$, the daily dosage may be reduced until there is evidence of marrow recovery; alternatively, recovery may be enhanced by brief (2-4 weeks) interruption of Zidovudine therapy. Marrow recovery is usually observed within 2 weeks after which time Zidovudine therapy at a reduced dosage may be reinstated. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (see section 4.3).

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 hyperlactataemia 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 (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). 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 (protease inhibitors) and lipodystrophy and NRTIs (nucleoside reverse transcriptase inhibitors) 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).

Liver disease: Zidovudine clearance in patients with mild hepatic impairment without cirrhosis [Child-Pugh scores of 5-6] is similar to that seen in healthy subjects, therefore no zidovudine dose adjustment is required. In patients with moderate to severe liver disease [Child-Pugh scores of 7-15], specific

dosage recommendations cannot be made due to the large variability in zidovudine exposure observed, therefore zidovudine use in this group of patients is not recommended.

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).

Immune reactivation syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 combination antiretroviral therapy. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Patients should be cautioned about the concomitant use of self-administered medications (see section 4.5).

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

Use in elderly and in patients with renal or hepatic impairment: See section 4.2.

Osteonecrosis: Although the etiology 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.

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 $48\% \pm 34\%$. This may result in a partial loss or total loss of efficacy of zidovudine. The concomitant use of rifampicin with zidovudine should be avoided (see section 4.4).

Zidovudine in combination with stavudine is antagonistic *in vitro*. The concomitant use of stavudine with zidovudine should be avoided (see section 4.4).

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, 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 $35\% \pm 23\%$ increase in plasma zidovudine AUC. The mode of interaction is unknown and as higher concentrations of atovaquone can be achieved with atovaquone suspension it is possible that greater changes in the AUC values for zidovudine might be induced when atovaquone is administered as a suspension. 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.

Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole, aerosolised pentamidine, pyrimethamine and aciclovir at doses used in prophylaxis.

Clarithromycin tablets reduce the absorption of zidovudine. This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.

4.6 Pregnancy and lactation

Pregnancy:

The use of zidovudine 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/mm³ (median in treated group 560/mm³) 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 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 section 5.3). The relevance of these findings to both infected and uninfected infants exposed to zidovudine is unknown. However, pregnant women considering using zidovudine during pregnancy should be made aware of these findings.

Given the limited data on the general use of zidovudine in pregnancy, zidovudine 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 on human female fertility. In men, zidovudine has 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 do not breast-feed their infants.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of zidovudine 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 reaction profile of Zidovudine should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The adverse reaction 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 (1200-1500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts less than 100/mm³. Dosage reduction or cessation of therapy may become necessary (see section 4.4).

The incidence of neutropenia was also increased in those patients whose neutrophil counts haemoglobin levels and serum vitamin B₁₂ levels were low at the start of zidovudine therapy.

The following events have been reported in patients treated with zidovudine.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency.

Assessment of frequencies:

Very common ($\geq 1/10$),

Common ($\geq 1/100$ to $<1/10$),

Uncommon ($\geq 1/1,000$ to $<1/100$),

Rare ($\geq 1/10,000$ to $<1/1,000$),

Very rare ($<1/10,000$), not known (cannot be estimated from the available data)

Cardiac disorders

Rare: Cardiomyopathy.

Blood and lymphatic system disorders

Common: Anaemia, neutropenia and leucopenia.

Uncommon: Pancytopenia with bone marrow hypoplasia, thrombocytopenia.

Rare: Pure red cell aplasia.

Very rare: Aplastic anaemia.

Nervous system disorders

Very common: Headache.

Common: Dizziness.

Rare: Convulsions, loss of mental acuity, insomnia, paraesthesia, somnolence.

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea.

Rare: Cough.

Gastrointestinal disorders

Very common: Nausea.

Common: Vomiting, diarrhoea and abdominal pain.

Uncommon: Flatulence.

Rare: Pancreatitis, oral mucosa pigmentation, taste disturbance and dyspepsia.

Renal and urinary disorders

Rare: Urinary frequency.

Skin and subcutaneous tissue disorders

Uncommon: Rash and pruritus.

Rare: Urticaria, nail and skin pigmentation and sweating.

Musculoskeletal and connective tissue disorders

Common: Myalgia.

Uncommon: Myopathy.

Metabolism and nutrition disorders

Rare: Lactic acidosis in the absence of hypoxaemia, anorexia.

General disorders and administration site conditions

Common: Malaise.

Uncommon: Asthenia, fever and generalised pain.

Rare: Chest pain and influenza-like syndrome, chills.

Hepatobiliary disorders

Common: Raised blood activities of liver-derived enzymes and bilirubin concentration.

Rare: Liver disorders such as severe hepatomegaly with steatosis.

Reproductive system and breast disorders

Rare: Gynaecomastia.

Psychiatric disorders

Rare: Anxiety and depression.

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 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 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 therapy. Other clinical adverse reactions and laboratory test abnormalities were similar in the zidovudine and placebo groups. It is unknown whether there are any long-term consequences of in utero and infant exposure to zidovudine.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

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).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4.).

4.9 Overdose

Symptoms and signs:

No specific symptoms or signs have been identified following acute overdose with zidovudine apart from those listed as undesirable effects 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 g there were no short term clinical, biochemical or haematological sequelae identified.

Treatment:

Patients should be observed closely for evidence of toxicity (see section 4.8) 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 catalyzed 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 characterized 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 characterized 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 zidovudine as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

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 a day) to HIV-positive pregnant women (from week 14-34 of pregnancy) and their newborn infants (2 mg/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 regimens 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

Adults

Absorption:

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 300 mg tablets 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.

Distribution:

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours, the mean total body clearance was 27.1 ml/min/kg and the apparent volume of distribution was 1.6 litres/kg.

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.

Plasma protein binding is relatively low (34 to 38%) and drug interactions involving binding site displacement are not anticipated.

Metabolism:

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated 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.

Excretion:

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

Paediatrics**Absorption:**

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 4.45 μ M (1.19 μ g/ml) following a dose of 120 mg zidovudine (in solution)/m² body surface area and 7.7 μ M (2.06 μ g/ml) at 180 mg/m² body surface area. Dosages of 180 mg/m² four times daily in children produced similar systemic exposure (24 hour AUC 40.0 hr μ M or 10.7 hr μ g/ml) as doses of 200 mg six times daily in adults (40.7 hr μ M or 10.9 hr μ g/ml).

Distribution:

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

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

Metabolism:

The major metabolite is 5'-glucuronide. After intravenous dosing, 29% of the dose was recovered unchanged in the urine and 45% excreted as the glucuronide.

Excretion:

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.

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.

Elderly:

No specific data are available on the pharmacokinetics of zidovudine in the elderly.

Renal impairment:

There are limited data on the pharmacokinetics of zidovudine in patients with renal impairment (see section 4.2).

Hepatic impairment:

There are limited data on the pharmacokinetics of zidovudine in patients with hepatic impairment (see section 4.2).

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. A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that fetuses exposed in utero to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

Carcinogenicity:

In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. 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

Capsule contents

Microcrystalline cellulose
Starch pregelatinised (maize)
Sodium starch glycolate (Type A)
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide (E171)
Sodium lauryl sulfate

Printing ink

Shellac
Dehydrated alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Strong Ammonia solution

Black iron oxide (E172)

Potassium hydroxide

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Blisters- Store in the original packaging

Bottles- Store in the original container

6.5 Nature and contents of container

Zidovudine 100 mg capsules, hard are available in PVC/PE/PVDC- Aluminum foil blister packs, containing 60 (6 X 10) and 100 (10 X 10) capsules and HDPE container containing 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited,
Ares, Odyssey Business Park,
West End Road,
South Ruislip HA4 6QD,
United Kingdom.
Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795

8 MARKETING AUTHORISATION NUMBER(S)

PL 20532/0100

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/08/2008

10 DATE OF REVISION OF THE TEXT

01/08/2008

Zidovudine 250mg capsules, hard

1 NAME OF THE MEDICINAL PRODUCT

Zidovudine 250 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg of zidovudine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

White/white size '0' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'D' on white cap and '73' on white body with black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Zidovudine 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

Oral use.

Zidovudine should be prescribed by physicians who are experienced in the treatment of HIV infection.

Dosage in adults:

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

Dosage in children:

3 months - 12 years:

The recommended dose of Zidovudine is 360 to 480 mg/m² 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.

Less than 3 months:

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

Dosage in the prevention of maternal-foetal transmission:

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 one hour followed by a continuous intravenous infusion at 1 mg/kg/h until 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). Infants unable to receive oral dosing should be given zidovudine intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours.

If a caesarean childbirth is planned then an intravenous form of zidovudine should be started 4 hours before the operation.

In the event of a false labour, then the zidovudine infusion should be stopped and oral dosing restarted. Refer to local, official guidelines for administration of zidovudine to neonates born to HIV-positive women.

Dosage adjustments in patients with haematological adverse reactions:

Substitution of zidovudine should be considered in patients whose haemoglobin level or neutrophil count fall to clinically significant levels. Other potential causes of anaemia or neutropenia should be excluded. Dose reduction or interruption of Zidovudine should be considered in the absence of alternative treatments (see sections 4.3 and 4.4).

Dosage in the elderly:

Zidovudine pharmacokinetics has 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 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 300-400 mg 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. For patients with end-stage renal disease maintained on haemodialysis or peritoneal dialysis, the recommended dose is 100 mg every 6-8 hours (300 mg – 400 mg daily)

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, due to the large variability in zidovudine exposures in patients with moderate to severe liver disease, 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 (see section 4.4).

4.3 Contraindications

- Hypersensitivity to zidovudine or to any of the excipients.
- Zidovudine should not be given to patients with abnormally low neutrophil counts (less than 0.75×10^9 /litre) or abnormally low haemoglobin levels (less than 7.5 g/decilitre or 4.65 mmol/litre).
- Zidovudine is contra-indicated in newborn 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 is not a cure for HIV infection or AIDS. Patients receiving Zidovudine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection.

The concomitant use of rifampicin or stavudine with zidovudine should be avoided (see section 4.5).

Haematological adverse reactions: Anaemia (usually not observed before six weeks of Zidovudine 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. 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 (see section 4.8).

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. 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 $0.75 \times 10^9/l$ and $1.0 \times 10^9/l$, the daily dosage may be reduced until there is evidence of marrow recovery; alternatively, recovery may be enhanced by brief (2-4 weeks) interruption of Zidovudine therapy. Marrow recovery is usually observed within 2 weeks after which time Zidovudine therapy at a reduced dosage may be reinstated. In patients with significant anaemia, dosage adjustments do not necessarily eliminate the need for transfusions (see section 4.3).

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 hyperlactataemia 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 (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). 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 (protease inhibitors) and lipodystrophy and NRTIs (nucleoside reverse transcriptase inhibitors) 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).

Liver disease: Zidovudine clearance in patients with mild hepatic impairment without cirrhosis [Child-Pugh scores of 5-6] is similar to that seen in healthy subjects, therefore no zidovudine dose adjustment is required. In patients with moderate to severe liver disease [Child-Pugh scores of 7-15], specific dosage recommendations cannot be made due to the large variability in zidovudine exposure observed, therefore zidovudine use in this group of patients is not recommended.

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).

Immune reactivation syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 combination antiretroviral therapy. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Patients should be cautioned about the concomitant use of self-administered medications (see section 4.5).

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

Use in elderly and in patients with renal or hepatic impairment: See section 4.2.

Osteonecrosis: Although the etiology 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.

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 $48\% \pm 34\%$. This may result in a partial loss or total loss of efficacy of zidovudine. The concomitant use of rifampicin with zidovudine should be avoided (see section 4.4).

Zidovudine in combination with stavudine is antagonistic *in vitro*. The concomitant use of stavudine with zidovudine should be avoided (see section 4.4).

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, 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 $35\% \pm 23\%$ increase in plasma zidovudine AUC. The mode of interaction is unknown and as higher concentrations of atovaquone can be achieved with atovaquone suspension it is possible that greater changes in the AUC values for zidovudine might be induced when atovaquone is administered as a suspension. 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.

Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole, aerosolised pentamidine, pyrimethamine and aciclovir at doses used in prophylaxis.

Clarithromycin tablets reduce the absorption of zidovudine. This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.

4.6 Pregnancy and lactation

Pregnancy:

The use of zidovudine 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/mm³ (median in treated group 560/mm³) 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 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 section 5.3). The relevance of these findings to both infected and uninfected infants exposed to zidovudine is unknown. However, pregnant women considering using zidovudine during pregnancy should be made aware of these findings.

Given the limited data on the general use of zidovudine in pregnancy, zidovudine 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 on human female fertility. In men, zidovudine has 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 do not breast-feed their infants.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of zidovudine 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 reaction

profile of Zidovudine should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The adverse reaction 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 (1200-1500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts less than 100/mm³. Dosage reduction or cessation of therapy may become necessary (see section 4.4).

The incidence of neutropenia was also increased in those patients whose neutrophil counts haemoglobin levels and serum vitamin B₁₂ levels were low at the start of zidovudine therapy.

The following events have been reported in patients treated with zidovudine.

The adverse reactions considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency.

Assessment of frequencies:

Very common ($\geq 1/10$),

Common ($\geq 1/100$ to $<1/10$),

Uncommon ($\geq 1/1,000$ to $<1/100$),

Rare ($\geq 1/10,000$ to $<1/1,000$),

Very rare ($<1/10,000$), not known (cannot be estimated from the available data)

Cardiac disorders

Rare: Cardiomyopathy.

Blood and lymphatic system disorders

Common: Anaemia, neutropenia and leucopenia.

Uncommon: Pancytopenia with bone marrow hypoplasia, thrombocytopenia.

Rare: Pure red cell aplasia.

Very rare: Aplastic anaemia.

Nervous system disorders

Very common: Headache.

Common: Dizziness.

Rare: Convulsions, loss of mental acuity, insomnia, paraesthesia, somnolence.

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea.

Rare: Cough.

Gastrointestinal disorders

Very common: Nausea.

Common: Vomiting, diarrhoea and abdominal pain.

Uncommon: Flatulence.

Rare: Pancreatitis, oral mucosa pigmentation, taste disturbance and dyspepsia.

Renal and urinary disorders

Rare: Urinary frequency.

Skin and subcutaneous tissue disorders

Uncommon: Rash and pruritus.

Rare: Urticaria, nail and skin pigmentation and sweating.

Musculoskeletal and connective tissue disorders

Common: Myalgia.

Uncommon: Myopathy.

Metabolism and nutrition disorders

Rare: Lactic acidosis in the absence of hypoxaemia, anorexia.

General disorders and administration site conditions

Common: Malaise.

Uncommon: Asthenia, fever and generalised pain.

Rare: Chest pain and influenza-like syndrome, chills.

Hepatobiliary disorders

Common: Raised blood activities of liver-derived enzymes and bilirubin concentration.

Rare: Liver disorders such as severe hepatomegaly with steatosis.

Reproductive system and breast disorders

Rare: Gynaecomastia.

Psychiatric disorders

Rare: Anxiety and depression.

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 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 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 therapy. Other clinical adverse reactions and laboratory test abnormalities were similar in the zidovudine and placebo groups. It is unknown whether there are any long-term consequences of in utero and infant exposure to zidovudine.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

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).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4.).

4.9 Overdose

Symptoms and signs:

No specific symptoms or signs have been identified following acute overdose with zidovudine apart from those listed as undesirable effects 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 g there were no short term clinical, biochemical or haematological sequelae identified.

Treatment:

Patients should be observed closely for evidence of toxicity (see section 4.8) 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 catalyzed 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 characterized 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 characterized 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 zidovudine as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

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 a day) to HIV-positive pregnant women (from week 14-34 of pregnancy) and their newborn infants (2 mg/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 regimens 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

Adults

Absorption:

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 300 mg tablets 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.

Distribution:

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours, the mean total body clearance was 27.1 ml/min/kg and the apparent volume of distribution was 1.6 litres/kg.

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.

Plasma protein binding is relatively low (34 to 38%) and drug interactions involving binding site displacement are not anticipated.

Metabolism:

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated 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.

Excretion:

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

Paediatrics

Absorption:

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 120 mg zidovudine (in solution)/m² body surface area and 7.7µM (2.06µg/ml) at 180 mg/m² body surface area. Dosages of 180 mg/m² four times daily in children produced similar systemic exposure (24 hour AUC

40.0 hr μM or 10.7 hr $\mu\text{g/ml}$) as doses of 200 mg six times daily in adults (40.7 hr μM or 10.9 hr $\mu\text{g/ml}$).

Distribution:

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

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

Metabolism:

The major metabolite is 5'-glucuronide. After intravenous dosing, 29% of the dose was recovered unchanged in the urine and 45% excreted as the glucuronide.

Excretion:

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.

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.

Elderly:

No specific data are available on the pharmacokinetics of zidovudine in the elderly.

Renal impairment:

There are limited data on the pharmacokinetics of zidovudine in patients with renal impairment (see section 4.2).

Hepatic impairment:

There are limited data on the pharmacokinetics of zidovudine in patients with hepatic impairment (see section 4.2).

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. A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that fetuses exposed in utero to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and

showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

Carcinogenicity:

In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. 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

Capsule contents

Microcrystalline cellulose
Starch pregelatinised (maize)
Sodium starch glycolate (Type A)
Magnesium stearate

Capsule shell

Gelatin
Titanium dioxide (E171)
Sodium lauryl sulfate

Printing ink

Shellac
Dehydrated alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Strong Ammonia solution
Black iron oxide (E172)
Potassium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Blisters- Store in the original packaging

Bottles- Store in the original container

6.5 Nature and contents of container

Zidovudine 250 mg capsules, hard are available in PVC/PE/PVDC- Aluminum foil blister packs, containing 40 (4 X 10) capsules and HDPE container containing 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20532/0101

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/08/2008

10 DATE OF REVISION OF THE TEXT

01/08/2008

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zidovudine 100 mg capsules, hard Zidovudine 250 mg capsules, hard Zidovudine

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Zidovudine is and what it is used for
2. Before you take Zidovudine
3. How to take Zidovudine
4. Possible side effects
5. How to store Zidovudine capsules, hard
6. Further information

1. WHAT ZIDOVUDINE IS AND WHAT IT IS USED FOR

Zidovudine capsules, hard contains the active ingredient zidovudine, which belongs to a group of medicines called antiretrovirals. It slows down the progression of human immunodeficiency virus (HIV) infection, which can lead to Acquired Immune Deficiency Syndrome (AIDS), in both adults and children.

Zidovudine is used in combination with other antiretrovirals, for the treatment of HIV infected adults and children.

Zidovudine is used in HIV positive pregnant women for preventing the transmission of the virus from mother to child.

2. BEFORE YOU TAKE ZIDOVUDINE

Do not take Zidovudine Capsules, hard

- if you are allergic (hypersensitive) to zidovudine or any other ingredients of Zidovudine capsules, hard.
- if you are anaemic (causing breathlessness on exertion or making you look pale) or have a low number of cells that fight infection (making you prone to infection).
- Zidovudine must not be given to some new-born babies with liver problems, including:
 - some cases of hyperbilirubinaemia (increased amounts in the blood of a substance called bilirubin which may make the skin appear yellow)
 - other problems which cause high levels of liver enzymes in the blood.

Take special care with Zidovudine

- if your bone marrow is compromised, which increases the risk of bleeding, bruising or infections.
- if you have liver or kidney problems.
- if you have any physical signs of fat redistribution, accumulation or loss of body fat.

Please speak with your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk of severe and potentially fatal liver adverse events and may require blood tests for monitoring of liver function.

Remember that treatment with zidovudine does not reduce the risk of passing HIV on to others by sexual contact or blood transfer. You should continue to use appropriate precautions to prevent this.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

An interaction means that medicines used at the same time can influence the effect(s) and/or side effect(s) of each other. An interaction can occur during the use of zidovudine with:

- **Rifampicin** (an antibiotic used for several serious infections) and stavudine (antiretroviral drug) may reduce the efficacy of zidovudine.
- **Lamivudine** (antiretroviral drug) and **Probenecid** (used to treat gout) increases absorption of zidovudine.
- **Phenytoin** (used to treat epilepsy) blood concentrations may alter when administered along with zidovudine.
- **Allopathic** (used to treat lung infections), **valproic acid** (used to treat seizure), **fluconazole** (used especially to treat fungal infections) and **methadone** (used for chronic pain management) increase the blood concentrations of zidovudine.
- Systemic **pentamidine** (used to treat lung infections), **dapsone** (used to treat leprosy), **pyrimethamine** (used in treatment of malaria), **co-trimoxazole** (an antibiotic), **amphotericin** (used to treat serious fungus infections), **flucytosine** (used to treat certain fungus infections), **ganciclovir** (used to treat infections caused by viruses) may increase the risk of adverse effects of zidovudine.
- Anticancer drugs such as interferon, **vincristine**, **vinblastine** and **doxorubicin** may increase the risk of adverse effects of zidovudine.
- **Clarithromycin** (antibacterial drug) reduce the absorption of zidovudine.

Please note that the above medicines may be known to you by other names, often the brand names. In this section only the active ingredient or therapeutic group of the medicine is given, and not the brand name. Always thoroughly check the pack and information leaflet of the medicines you are already using for the active ingredient or therapeutic group of that medicine.

Taking zidovudine with food and drink

Zidovudine may be taken with or without food.

Pregnancy and breast-feeding

Please see section 3 "How to take Zidovudine" under "Dosage during pregnancy and breast-feeding".

Pregnancy

Ask your doctor or pharmacist for advice before using any medicine.

Tell your doctor if you become pregnant or are trying to become pregnant, or you are breast-feeding.

Zidovudine can be taken by HIV-positive pregnant women (after the first three months of

pregnancy) to reduce the risk of transmitting HIV to their unborn child. If you are prescribed zidovudine earlier than 14 weeks, your doctor will have weighed up the expected benefits to you against any possible risks to your unborn baby.

Zidovudine is given to the woman up to and during labour and is stopped after delivery.

Note that while use of Zidovudine during pregnancy can reduce the chance that your baby will get HIV; some may get it even with this treatment.

Breast-feeding

Ask your doctor or pharmacist for advice before using any medicine.

Zidovudine passes into breast milk, so it is recommended that mothers taking this medicine do not breastfeed. Breastfeeding may also increase the risk of passing on the HIV virus to the baby.

Driving and using machines

There is no data to suggest that zidovudine affects ability to drive or operate machinery. Be careful driving or operating machinery until you know how treatment with zidovudine affects you.

3. HOW TO TAKE ZIDOVUDINE

Always take zidovudine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dosage in adults:

The usual total daily dose is 500 mg to 600 mg, taken in smaller doses two to three times during the day.

Dosage in children:

3 months - 12 years:

The recommended dose is 360 to 480 mg/m² per day in 3 or 4 divided doses. The maximum dosage should not be more than 200 mg every 6 hours.

Dosage during pregnancy and delivery:

Zidovudine is not recommended to be given if you are less than 14 weeks through your pregnancy. After the fourteenth week, your doctor may tell you to take 500 mg per day until the beginning of your delivery.

Dosage adjustments in patients with blood related adverse reactions:

Your doctor will recommend an alternative treatment if you have low haemoglobin concentrations or low number of white blood cells, and in the absence of alternative treatment your doctor will reduce the dose or stop the treatment.

Dosage in the elderly:

Special care is advised in this age group and appropriate monitoring of patients before and during use of zidovudine is advised.

Dosage in patient with kidney problems:

Your doctor may decide to use a lower dose of 300 mg to 400 mg per day in 3 to 4 divided doses, depending on how well your kidneys are working.

Dosage in hepatic impairment:

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

If you take more zidovudine than you should

Accidentally taking too much zidovudine is unlikely to cause any serious problems. However, you should tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

If you forget to take zidovudine

It is important to take the total daily dose prescribed to ensure you get maximum benefit. If you forget to take a dose of your medicine, take it as soon as you remember, and then continue as before.

Do not take a double dose to make up for a forgotten dose.

If you stop taking zidovudine

Because your medicine controls and does not cure your condition, you will normally need to take it continuously. You should not stop treatment unless your doctor tells you to.

4. POSSIBLE SIDE EFFECTS

Like all medicines, zidovudine can cause side effects, although not everybody gets them.

The following side effects have been observed:

Very Common (Affecting at least 1 of each 10 patients)

- headache
- feeling sick (nausea)

Common (Affecting at least 1 of each 100 patients)

- anaemia, which may cause weakness and shortness of breath
- reduced number of cells that fight infection, which can make you more prone to infection
- dizziness
- being sick (vomiting)
- stomach pain and diarrhoea
- liver disorders e.g. jaundice
- muscle pain
- tiredness, generally feeling unwell

Uncommon (Affecting at least 1 of each 1,000 patients)

- reduction in blood platelets, which increases risk of bleeding or bruising
- difficulty in breathing
- trapped air in the stomach
- rash and itching
- pain or weakness in muscle
- weakness, fever and generalised pain

Rare (Affecting at least 1 of each 10,000 patients)

- failure to develop red blood cells, which may cause tiredness or breathlessness
- loss of appetite and build up of lactic acid level in the body, that can cause dehydration and coma
- anxiety and depression
- sleeplessness (insomnia)

- pins and needles sensation, sleepiness, inability to concentrate and fits
- disease of the heart muscles (cardiomyopathy). Symptoms of this may include shortness of breath, swelling of your ankles or fluid in your lungs.
- cough
- changes in skin colour inside the mouth
- taste disturbances
- indigestion
- inflammation of pancreas
- liver disorders such as enlarged liver, fatty liver
- Nail and skin colour changes
- rash (red, raised or itchy)
- sweating
- increased need to urinate (pass water)
- enlarged breasts in male patients
- chest pain
- "flu-like" feeling
- chills

Very Rare (Affecting less than 1 out of 10,000 patients*)

- severe reduction in blood cells which can cause weakness, bruising or make infections more likely

Other possible side effects of combination therapy for HIV:**Old infections may flare up**

People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.

If you get any symptoms of infection while you're taking Zidovudine:

Tell your doctor immediately. Don't take other medicines for the infection without your doctor's advice.

Your body shape may change

People taking combination therapy for HIV may find that their body shape changes, because of changes in fat distribution:

- Fat may be lost from the legs, arms or face.
- Extra fat may build up around the tummy (abdomen), or on the breasts or internal organs.
- Fatty lumps (sometimes called buffalo hump) may appear on the back of the neck.

It is not yet known what causes these changes, or whether they have any long-term effects on your health. If you notice changes in your body shape:

Tell your doctor.

Lactic acidosis is a rare but serious side effect

Some people taking Zidovudine, or other medicines like it (NRTIs), develop a condition called lactic acidosis, together with an enlarged liver. Lactic acidosis is caused by a build-up of lactic acid in the body. It is rare; if it happens, it usually develops after a few months of treatment. It can be life-threatening, causing failure of internal organs.

Lactic acidosis is more likely to develop in people who have liver disease, or in obese (very overweight) people, especially women.

Signs of lactic acidosis include:

- deep, rapid, difficult breathing
- drowsiness
- numbness or weakness in the limbs
- feeling sick (nausea), being sick (vomiting)
- stomach pain.

During your treatment, your doctor will monitor you for signs of lactic acidosis. If you have any of the symptoms listed above, or any other symptoms that worry you:

See your doctor as soon as possible.

You may have problems with your bones

Some people taking combination therapy for HIV develop a condition called osteonecrosis. With this condition, parts of the bone tissue die because of reduced blood supply to the bone.

People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Symptoms of osteonecrosis include:

- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:

Tell your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ZIDOVUDINE CAPSULES, HARD

Keep out of the reach and sight of children.

Do not use Zidovudine capsules, hard after the expiry date, which is stated on the carton/label after EXP. The expiry date refers to the last day of that month.

Blisters- Store in the original packaging

Bottles- Store in the original container

Do not use Zidovudine capsules, hard if you notice visible signs of deterioration.

Medicines should not be disposed off via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION**What Zidovudine capsules, hard contains**

- The active substance is zidovudine. Each capsule contains 100 mg/250 mg of zidovudine.
- The other ingredients are:

Capsule contents: Microcrystalline cellulose, starch pregelatinised (maize), sodium starch glycolate (Type A) and magnesium stearate.

Capsule shell: Gelatin, titanium dioxide (E 171) and sodium lauryl sulfate.

Printing ink: Shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide (E172), potassium hydroxide and purified water.

What Zidovudine capsules, hard looks like and contents of the pack

Capsule, hard.

Zidovudine 100 mg capsules, hard are white/white size '3' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'D' on white cap and '01' on white body with black ink.

Zidovudine 250 mg capsules, hard are white/white size '0' hard gelatin capsules filled with white to off-white granular powder and imprinted with 'D' on white cap and '73' on white body with black ink.

Zidovudine 100 mg capsules, hard are available in blister packs of 60 (6 X 10), 100 (10 X 10) capsules and HDPE container containing 100 capsules.

Zidovudine 250 mg capsules, hard are available in blister packs of 40 (4 X 10) capsules and HDPE container containing 100 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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South Ruislip HA4 6QD
United Kingdom
Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795

This medicinal product is authorised in the Member States of the EEA under the following names:

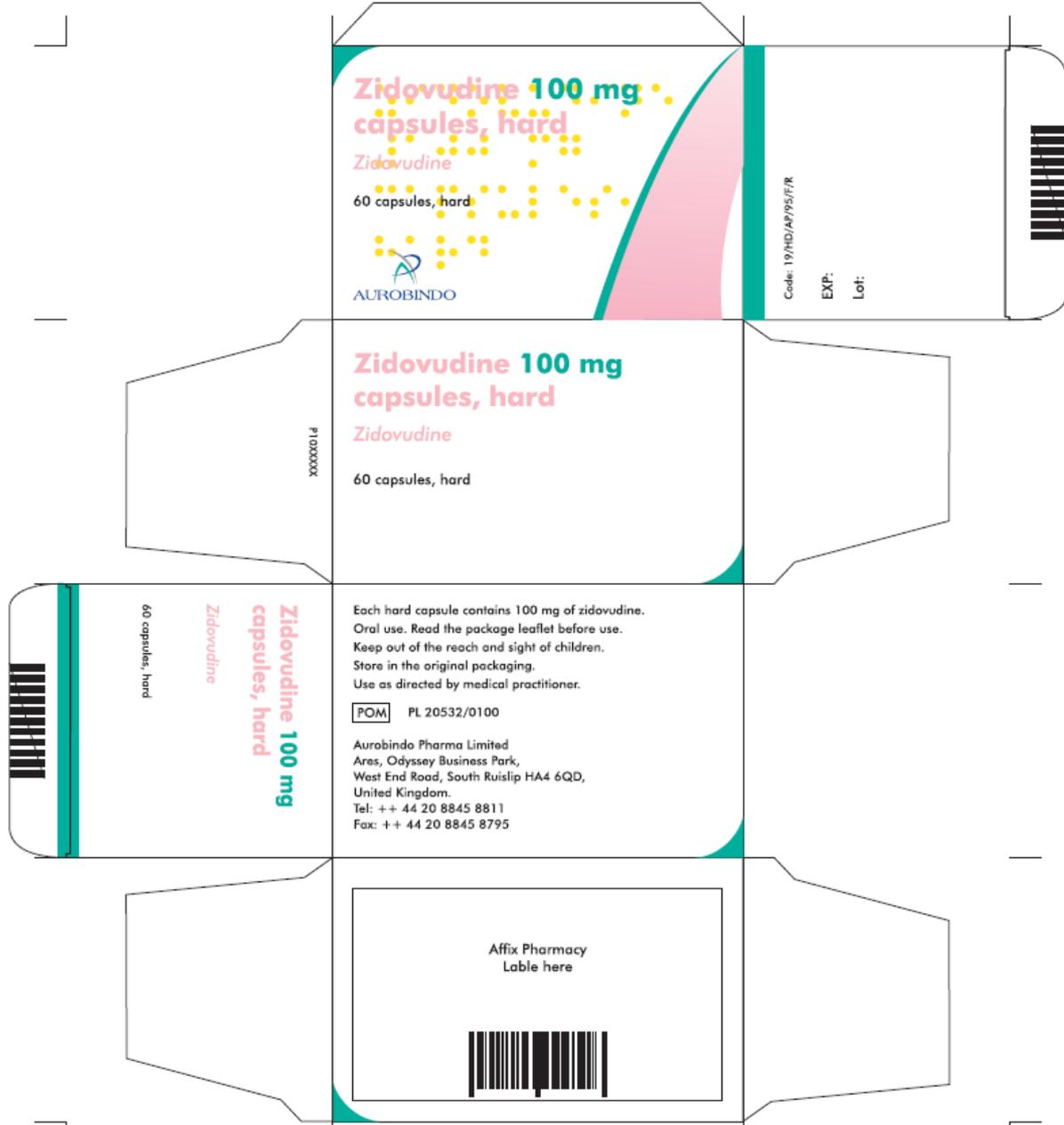
Belgium	Zidovudine Aurobindo 100 mg/250 mg gélules
Germany	Zidovudin Aurobindo 100 mg/250 mg Hartkapseln
France	ZIDOVUDINE AUROBINDO 100 mg/250 mg, gélules
Spain	ZIDOVUDINA AUROBINDO 100 mg/250 mg cápsulas duras
United Kingdom	Zidovudine 100 mg/250 mg capsules, hard

This leaflet was last approved in 07/2008.

Module 4

Labelling

100mg strength - Blister carton - pack size 60 capsules

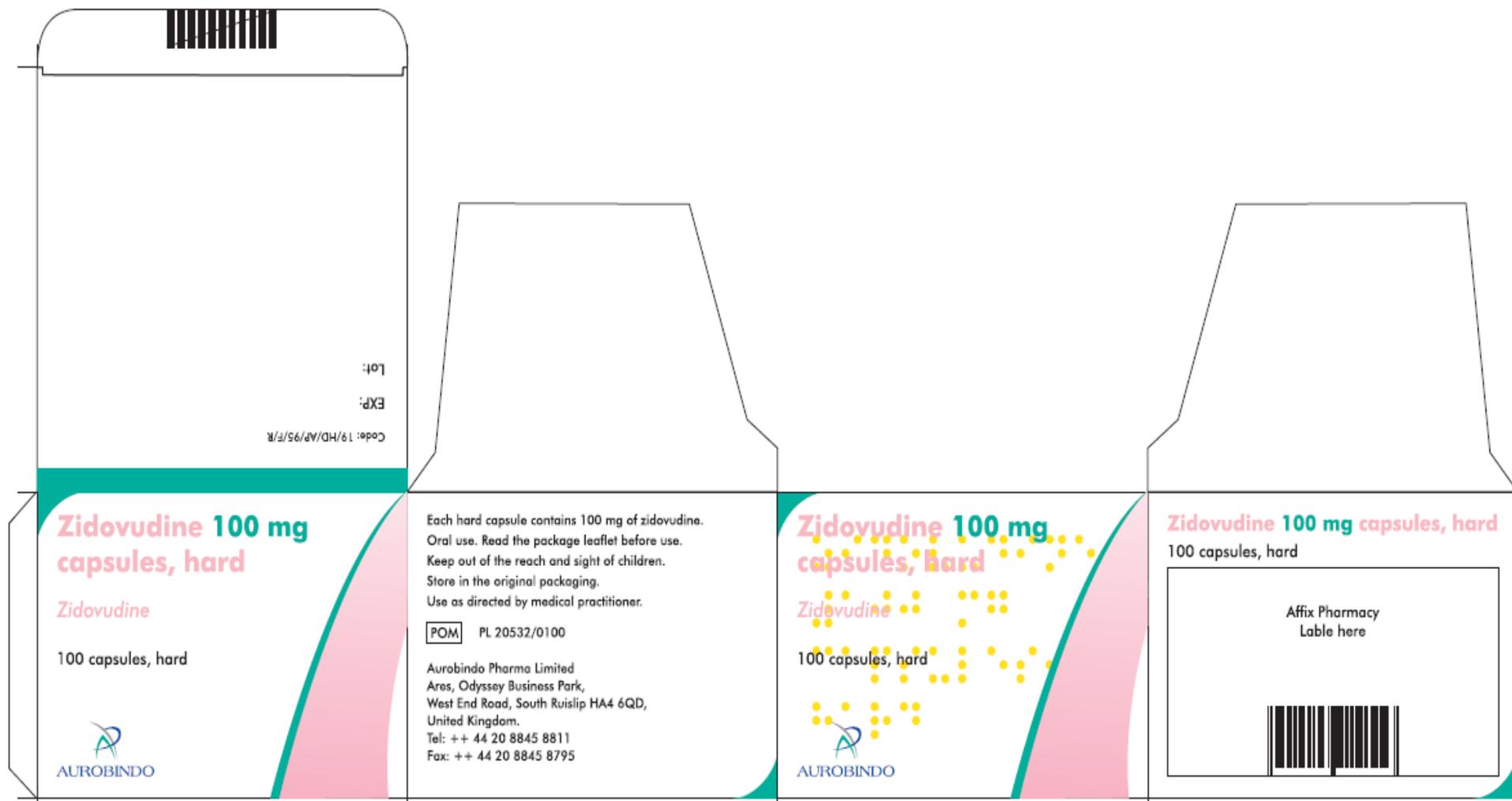


Translation of Braille on both 100mg strength blister cartons

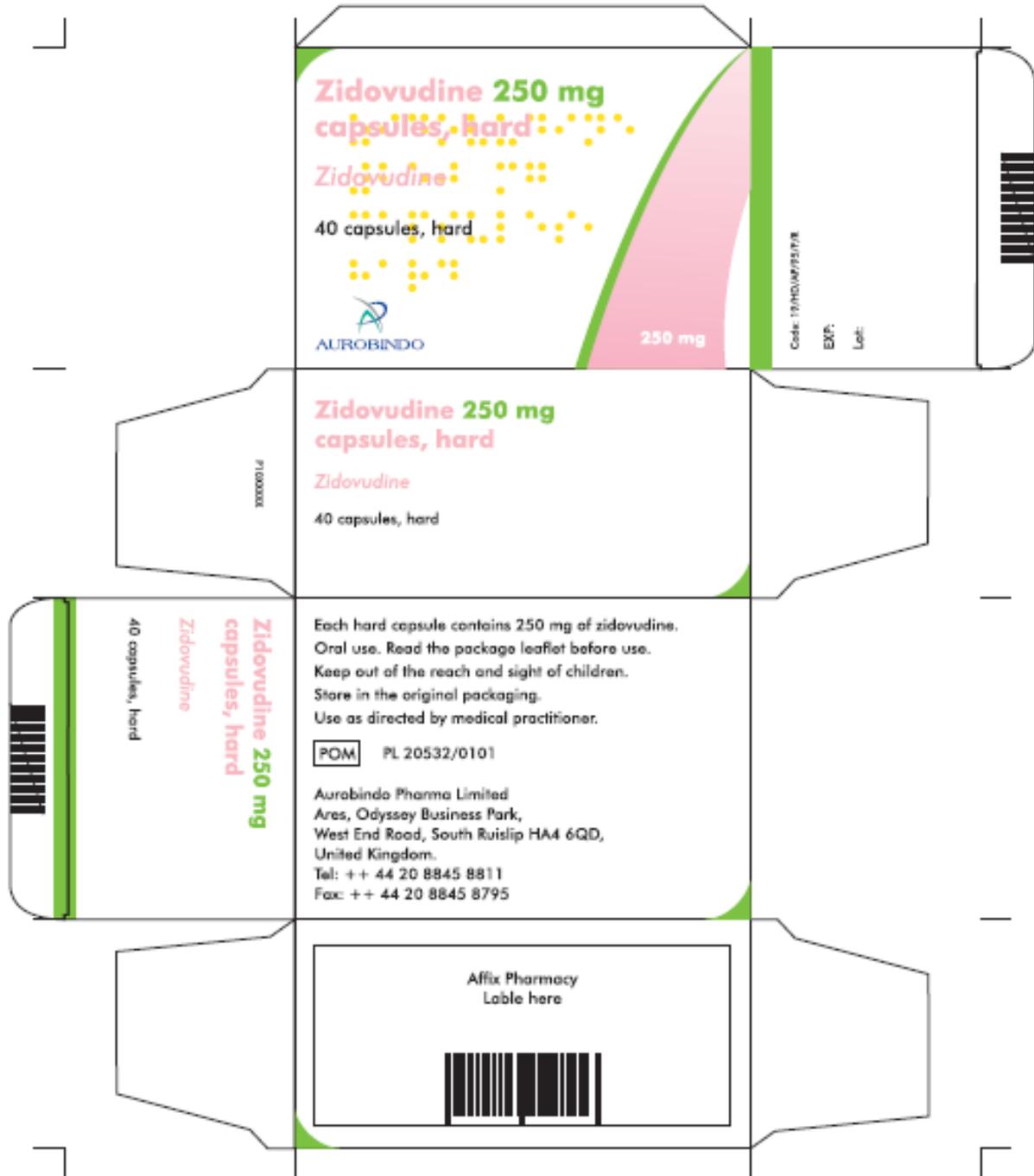


Zidovudine
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sign. 100 mg
capsules,
hard

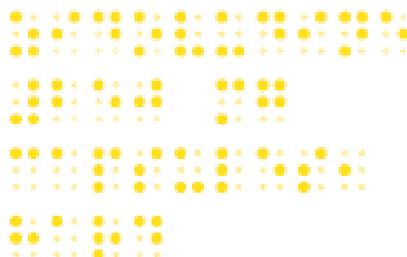
100mg strength - Blister carton - pack size 100 capsules



250mg strength - Blister carton - pack size 60 capsules



Translation of Braille on 250mg strength blister carton



Zidovudine
nr
sign. 250 mg
capsules,
hard

Blister foils

Zidovudine 100 mg capsules, hard
Zidovudine Aurobindo Pharma Limited

Zidovudine 100 mg capsules, hard
Zidovudine Aurobindo Pharma Limited

Zidovudine 100 mg capsules, hard
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Zidovudine Aurobindo Pharma Limited

Zidovudine 250 mg capsules, hard
Zidovudine Aurobindo Pharma Limited

Zidovudine 250 mg capsules, hard
Zidovudine Aurobindo Pharma Limited

100mg strength - Bottle carton



Bottle label

Each hard capsule contains 100 mg of zidovudine.

Oral use. Read the package leaflet before use.

Keep out of the reach and sight of children.

Store in the original container. Use as directed by medical practitioner.

Zidovudine 100 mg capsules, hard

Zidovudine

100 capsules, hard

PL 20532/0100

POM

AUROBINDO

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Tel: ++ 44 20 8845 8811
Fax: ++ 44 20 8845 8795

Code: 19/HD/AP/95/F/R

Lot :
EXP :



Translation of Braille on bottle carton



Zidovudine
nr sign. **100 mg**
capsules, hard

250mg strength - Bottle carton



Bottle label

Each hard capsule contains 250 mg of zidovudine.
 Oral use. Read the package leaflet before use.
 Keep out of the reach and sight of children.
 Store in the original container.
 Use as directed by medical practitioner.

Zidovudine 250 mg capsules, hard

Zidovudine

100 capsules, hard

PL 20532/0101

POM

AUROBINDO

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Code: 19/HD/AP/95/F/R

Lot :
 EXP :



Translation of Braille on bottle carton



Zidovudine
 nr sign. 250 mg
 capsules, hard

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Aurobindo Pharma Limited Marketing Authorisations for the medicinal products Zidovudine 100mg and 250mg Capsules, hard (PL 20532/0100-0101, UK/H/1086/01-02/DC). The products are prescription-only medicines.

These are abridged applications for Zidovudine 100mg and 250mg Capsules, hard, two strengths of zidovudine, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the innovator products, Retrovir Capsules 100mg and 250mg respectively (PL 00003/0239 & 0240, The Wellcome Foundation Limited) that were granted UK licences on 03/03/1987. The reference products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Zidovudine 100mg and 250mg Capsules, hard contain the active ingredient, zidovudine, an anti-retroviral drug used in the treatment of HIV infection. It belongs to the class of Nucleoside Reverse Transcriptase Inhibitors. It is a potent *in vitro* inhibitor of Human Immunodeficiency Virus with varying efficacy against other retroviruses. Zidovudine may be used in monotherapy and in combination with other anti-retroviral medications to substantially reduce the risk of HIV infection following a significant exposure to the virus.

Zidovudine 100mg and 250mg Capsules, hard are indicated in anti-retroviral combination therapy for Human Immunodeficiency Virus (HIV) infected adults and children. The usual recommended adult dose of Zidovudine in combination with other anti-retroviral agents is 500 or 600 mg/day in two or three divided doses, and in children (3 months to 12 years) is 360 to 480 mg/m² per day, in 3 or 4 divided doses. The maximum dosage in children should not exceed 200 mg every 6 hours.

Zidovudine 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. Pregnant women (over 14 weeks of gestation) should be given 500 mg/day orally (100 mg five times per day/ 250mg two times per day) until the beginning of labour.

No new preclinical studies were conducted, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years. The application depends upon the bioequivalence study presented by the applicant comparing the test product, Zidovudine 250mg Capsules, to the reference product Retrovir 250mg Capsules (GlaxoSmithKline, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Zidovudine 100mg capsules, hard Zidovudine 250mg capsules, hard
Name(s) of the active substance(s) (INN)	Zidovudine
Pharmacotherapeutic classification (ATC code)	Nucleoside analogue (J05A F01)
Pharmaceutical form and strength(s)	100mg and 250mg capsules, hard
Reference numbers for the Mutual Recognition Procedure	UK/H/1086/01-02/DC
Reference Member State	United Kingdom
Member States concerned	Belgium, Germany, Spain, France
Marketing Authorisation Number(s)	PL 20532/0100-0101
Name and address of the authorisation holder	Aurobindo Pharma Limited, Ares, Odyssey Business Park, West End Road, South Ruislip HA4 6QD, United Kingdom.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

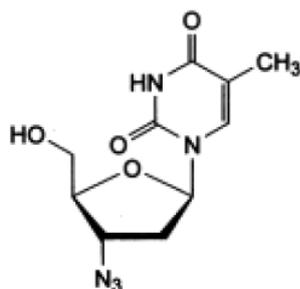
Zidovudine

Nomenclature:

INN: Zidovudine

Chemical name: 1-[(2*R*,4*S*,5*S*)-4-azido-5-(hydroxymethyl)tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione

Structure:



Molecular formula: C₁₀H₁₃N₅O₄

Molecular weight: 267.2

CAS No: 30516-87-1

Physical form: White or brownish powder

Solubility: Sparingly soluble in water, soluble in anhydrous ethanol

The active substance, zidovudine, is the subject of a European Pharmacopoeia (EP) monograph.

All aspects of the manufacture and control of zidovudine are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of zidovudine for inclusion in this medicinal product.

The active substance is stored in appropriate packaging. It is packed in a low-density polyethylene (LDPE) bag, which is closed with a twist tie with a plastic fastener. This bag is inserted into a second LDPE bag, which is also closed with a twist tie and plastic fastener. This pack is finally placed in a well-closed high-density polyethylene (HDPE) container. Specifications and Certificates of Analysis have been provided for the packaging materials used. The LDPE bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed packaging. These data demonstrate the stability of the active substance and a retest period of 2 years has been set. This is satisfactory.

DRUG PRODUCT

Description and Composition

The drug products are presented as hard capsules containing white to off-white granular powder (see SPCs / patient information leaflet for full descriptions of capsules). The granular powder contains 100mg or 250mg zidovudine in a single capsule.

Other ingredients consist of pharmaceutical excipients, namely pregelatinised maize starch, microcrystalline cellulose, magnesium stearate, and sodium starch glycolate making up the capsule contents; titanium dioxide (E171), sodium lauryl sulfate, and gelatin making up the capsule shell; and shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide (E172), potassium hydroxide, and purified water making up the printing ink. Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the capsule contents and capsule shells comply with their respective European Pharmacopoeia monograph. The excipients making up the printing ink comply with suitable specifications, as follows – shellac (NF), dehydrated alcohol (USP), isopropyl alcohol (USP), butyl alcohol (NF), propylene glycol (USP), strong ammonia solution (NF), black iron oxide – E172 (NF), potassium hydroxide (NF), and purified water (EP, USP), and are all EP compliant. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate and sodium lauryl sulfate are of vegetable origin. The only excipient used that contains material of animal or human origin is gelatin. A Certificate of Suitability has been provided by the supplier of gelatin stating that the gelatin they provide meets the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution profiles for the applicant’s test products (Zidovudine 100mg and 250mg Capsules, hard) were provided and were similar to each other. The dissolution profile for Zidovudine 250mg Capsules was shown to be similar to that of the UK reference product (Retrovir 250mg Capsules).

Impurity profiles were provided for Zidovudine 100mg and 250mg Capsules, hard, and all impurities were within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished products. The specifications are in line with Ph Eur requirements for capsules. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working reference standards used.

Container Closure System

Two types of primary packaging are proposed for the marketed product:

- (1) polyvinyl chloride / polyethylene / polyvinylidene chloride / aluminium blisters
- (2) HDPE containers with polypropylene closures

The capsules are packed in the blisters / HDPE containers, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The 100mg capsules are packaged in blister pack sizes of 60 (6 x 10) and 100 (10 x 10) capsules, and the 250mg capsules are packaged in blister pack sizes of 40 (4 x 10) capsules. Both the 100mg and 250mg strength capsules are packaged in HDPE container pack sizes of 100 capsules. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are 'Store in the original packaging' for the blister packs and 'Store in the original container' for the HDPE bottle packs.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Zidovudine 250mg capsules, to the reference product, Retrovir 250mg Capsules (GlaxoSmithkline, UK).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Expert Report

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory.

Conclusion

The test products are pharmaceutically equivalent to the reference products which have been licensed in at least one EU member state for over 10 years. The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Zidovudine 250mg capsules, hard is a generic medicinal product of Retrovir 250mg Capsules (GlaxoSmithKline, UK) appears justified.

As the test products, Zidovudine 100mg & 250mg capsules, hard, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 250mg strength were extrapolated to the 100mg strength capsules.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.

III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic versions of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacological and toxicological properties of zidovudine, which is a widely used and well-known active substance.

III.3 CLINICAL ASPECTS

INDICATIONS

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

Zidovudine 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.

The indications are consistent with those for the reference products and are satisfactory.

POSODOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of zidovudine is well known. No novel pharmacodynamic data are supplied or required for this application.

Pharmacokinetics

The applicant has conducted a single bioequivalence study comparing the pharmacokinetic profiles of Zidovudine 250mg capsules (test) and Retrovir 250mg Capsules, GlaxoSmithKline, UK (reference). The study was of an appropriate design and was conducted to principles of good clinical practice.

This was an open-label, randomised, two-treatment, two-period, two sequence, single dose crossover bioavailability and bioequivalence study conducted in 38 (37 completed) healthy adult human male subjects under fasting conditions.

A single dose of the investigational products was administered orally to each subject in each period with 240 ml of water, after an overnight fast. The subjects were then fasted for a further 4 hours after administration of dose. Water was not permitted for one hour before and for one hour after the dose was given. A 'standard meal' was given at 4 hours, 8 hours and 13 hours after the dose was administered. A washout period of 6 days was maintained between the two dosing days in each group. A washout out period of six days is acceptable as the mean half life of zidovudine is approximately 1 hour (0.78-1.93 hours).

Blood samples were taken at the following times (hours): pre-dose (0.0) and then at 0.167, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5,4.0,5.0, 6.0, 8.0 and 12.0 hours after administration of test or reference product. The samples were extracted and analysed by a validated LC-MS/MS method, which has an LOQ value of 10.08 ng/ml.

Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals fell within the acceptance range of 0.8-1.25 for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$.

Results:

Adverse events - One subject reported body pains in phase II. Six adverse events were laboratory test abnormalities found after the study.

Management of withdrawals and protocol deviations - One subject did not report for phase II of the study and was withdrawn. This complied with the protocol.

The summary of the results of the bioequivalence study are tabulated below.

Statistics		C_{max} (hr. ng/mL)	AUC_{0-t} (hr. ng/mL)	$AUC_{0-\infty}$ (hr. ng/mL)	T_{max} (hr)*	
Test Formulation Zidovudine 250mg capsules, Aurobindo Pharma Limited,	Mean (N=37)	1511.66	1986.31	2017.61	0.50	
	S.D.	661.197	498.263	500.613	0.258	
	C.V (%)	43.74	25.08	24.81	42.07	
Reference Formulation RETROVIR 250mg capsules, GlaxoSmithKline, UK	Mean (N=37)	1425.68	1951.12	1986.20	0.50	
	S.D.	628.264	481.810	484.411	0.183	
	C.V (%)	44.07	24.69	24.39	32.01	
Ratio (T/R %)	Lntransformed	106.23	101.78	101.55	--	
90 % Confidence Interval	Lntransformed	<i>Lower</i>	93.49	97.62	97.50	--
		<i>Upper</i>	120.72	106.11	105.77	--
Power (%)	Lntransformed	89	100	100	--	

* For T_{max} instead of mean, median has been used.

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test product and reference product are bioequivalent as the confidence intervals for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80-125% in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Zidovudine 100mg Capsules. As Zidovudine 100mg and 250mg Capsules, hard meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 250mg strength were extrapolated to the 100mg strength product.

Clinical efficacy

No new data have been submitted and none are required. Efficacy is reviewed in the clinical overview. The efficacy of zidovudine is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. Safety is reviewed in the clinical overview. The safety profile of zidovudine is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the innovator products, and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Zidovudine 250mg Capsules, Aurobindo) and reference (Retrovir 250mg Capsules, GlaxoSmithKline UK) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 250mg strength were extrapolated to the 100mg strength products.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, granted on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Zidovudine 100mg and 250mg Capsules, hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Zidovudine 250mg Capsules, and the reference product, Retrovir 250mg Capsules (PL 00003/0239, GlaxoSmithKline, UK).

As Zidovudine 100mg and 250mg Capsules, hard were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 250mg strength were extrapolated to the 100mg capsule strength, and no separate bioequivalence studies were necessary.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study, and the valid extrapolation of its results and conclusions, support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with zidovudine is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome