PUBLIC ASSESSMENT REPORT

Zidovudine Capsules 100 mg

International Nonproprietary Name (INN): **Zidovudine**

Abstract

Zidovudine Capsules 100 mg, supplied by Aurobindo Pharma, Ltd., Unit III, Survey No. 313, Bachupally, Quthubullapur, Mandal, Hyderabad, Andhra Pradesh, 500 072, India, was the subject of an Abbreviated New Drug Application (ANDA) submitted to the U. S. Food and Drug Administration (USFDA) pursuant to section 505(j) of the U. S. Federal Food, Drug, and Cosmetic Act.

This ANDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR). Based upon the information presented the USFDA concluded that Zidovudine Capsules 100 mg are safe and effective for use as recommended in the submitted labeling, and, accordingly, the application was **approved** on March 27, 2006. This determination was based on information available to the agency (i.e., information in the ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product).

On the basis of USFDA approval, Zidovudine Capsules 100 mg was placed with the footnote "USFDA" on the WHO Prequalification Programme list of manufacturers and suppliers whose HIV-related products have been found acceptable, in principle, for procurement by UN Agencies (WHO Prequalification Programme: Priority Essential Medicines, 63rd Edition, 1 February 2008).

Products listed on the WHO Prequalification Programme list with the note "USFDA" are added to the list based on scientific assessment and inspections conducted by the USFDA. Product listing as USFDA **approved** indicates that the product is eligible for purchase with PEPFAR funds.

Zidovudine Capsules 100 mg are indicated for the treatment of HIV infection. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (Part 4) and Scientific Discussion (Part 6) of this Public Assessment Report.

The active pharmaceutical ingredient (API) of Zidovudine capsules is the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine, a well established and documented product for the treatment of HIV/AIDS in combination with other products.

Zidovudine has been investigated in combination therapy in several clinical trials in both treatment-naïve and treatment-experienced patients. These studies have demonstrated significant decreases in HIV-1 viral load and increases in CD4 cell count. Clinical end-point data indicate that zidovudine in combination with other antiretroviral agents results in a significant reduction in the risk of disease progression and mortality.

The most commonly reported adverse events are headache, nausea, rash and itching, myalgia, malaise, anemia, leukopenia, neutropenia, and transient elevation of liver enzymes and bilirubin.

The most important safety problems with zidovudine are rare but severe lactic acidosis and hepatic steatosis with hepatic failure which could be fatal.

The risk/benefit profile of Zidovudine Capsules 100 mg showed an acceptable safety profile and adequate antiretroviral activity.

All Accepted Presentations

Status	USFDA Approved 9/19/2005
INN	Zidovudine
Strength	100 mg
Form	Capsules
Route of administration	Oral
Packaging	Bottles; unit-dose packages
Package size	Bottles of 100; 10x10 unit-dose packages

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zidovudine Capsules 100 mg

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, please ask your doctor, health care provider, or pharmacist.
- This medicine has been prescribed for you personally, and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.

In this leaflet:

1. WHAT ZIDOVUDINE CAPSULES ARE AND WHAT THEY ARE USED FOR

Zidovudine Capsules belongs to a group of antiviral medicines, also known as antiretrovirals, called nucleoside analogue reverse transcriptase inhibitors (NRTIs). These are used to treat Human Immunodeficiency Virus (HIV) infection.

Zidovudine Capsules are used in antiretroviral combination therapy for the treatment of HIV infection. Zidovudine Capsules reduces the amount of HIV virus in your body and keeps it at a low level. It also increases CD4 cell counts. (CD4 cells are a type of white blood cells that play an important role in maintaining a healthy immune system to help fight infection.)

Response to treatment with Zidovudine Capsules varies between patients. Your doctor or health care provider will monitor the effectiveness of your treatment. Zidovudine Capsules may improve your condition but are not a cure for your HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with Zidovudine Capsules has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

During your treatment, other infections linked to your weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. BEFORE YOU TAKE ZIDOVUDINE CAPSULES

Do not take Zidovudine Capsules if:
• You are allergic (hypersensitive) to zidovudine or any of the other ingredients of Zidovudine Capsules (see section 6, What Zidovudine Capsules contain)
• You have a very low red blood cell count (severe anemia) or very low white blood cell count (neutropenia).

Take special care with Zidovudine Capsules
Before using this medicine, tell your doctor or health care provider if you suffer from kidney disease or liver disease (such as hepatitis).

Anemia (low red blood cell count) and neutropenia or leukopenia (low white blood cell count) may occur within 4-6 weeks after starting treatment with Zidovudine Capsules. If severe, your doctor may stop treatment with Zidovudine Capsules. These side effects occur more commonly in patients with advanced HIV disease and with higher doses of zidovudine. Regular blood tests may need to be done to check for any problems related to your treatment with Zidovudine Capsules. These reactions are infrequent in patients with early HIV disease and blood tests may be performed less frequently.

The class of medicines to which Zidovudine Capsules belongs (NRTIs) can cause a rare but serious side effect called lactic acidosis, together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Lactic acidosis is a build-up of lactic acid in the body, which can cause dehydration and coma. Deep, rapid breathing, drowsiness, and nonspecific symptoms such as nausea, vomiting, and stomach pain, may indicate the development of lactic acidosis. Lactic acidosis may also lead to rare cases of renal failure, liver failure, or fatal hepatitis.

Lactic acidosis occurs more often in women, particularly if very overweight. If you have liver disease you may also be at greater risk of lactic acidosis. While you are taking Zidovudine Capsules, your doctor or health care provider will monitor you closely for any signs that you may be developing lactic acidosis.

Tell your doctor or health care provider if you have a history of liver disease. Patients with chronic hepatitis B or C who are treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests to monitor liver function.

If you have chronic hepatitis B infection, you should not stop your treatment without instructions from your doctor or health care provider, as you may have a recurrence of hepatitis. This recurrence may be more severe if you have serious liver disease.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection (infections that are more common in people with suppressed immune function), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, tell your doctor or health care provider immediately.

Accumulation, change in location, or loss of body fat may occur in patients receiving antiretroviral therapy. Tell your doctor or health care provider if you notice changes in body fat.

Take Zidovudine Capsules every day as prescribed by your doctor or healthcare professional. They help control your condition but are not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. Maintain regular contact with your doctor or health care provider. Do not stop taking your medicine without first talking to your doctor or health care provider.

Taking other medicines
Tell your doctor, health care provider, or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of Zidovudine Capsules, or Zidovudine Capsules may affect their action.

Zidovudine in any form, including Zidovudine Capsules, should not be taken in combination with stavudine or ribavirin.

Zidovudine in any form, including Zidovudine Capsules, may also interact with valproic acid, fluconazole, and probenecid, making side effects worse. The use of any of these drugs along with Zidovudine should be discussed with your doctor.

Taking Zidovudine at the same time with medicines that are potentially damaging to the kidneys or bone marrow (for example, systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, cidofovir, ganciclovir, valganciclovir, interferon, vincristine, vinblastine, or doxorubicin) may increase the risk of adverse reactions to zidovudine. If taking Zidovudine Capsules along with any of these other medicines is necessary, extra care should be taken in monitoring kidney function and blood cells, and, if necessary, the dosage of one or more medicines should be reduced. Talk with your doctor if you take any of the medicines mentioned above.

Taking Zidovudine Capsules with food and drink
Zidovudine Capsules may be taken with or without food

Pregnancy
If you become pregnant, or are planning to become pregnant, tell your doctor or health care provider to discuss the potential adverse effects and the benefits and risks of your antiretroviral therapy to you and your child.

If you have taken Zidovudine in any form during your pregnancy, your doctor or health care provider may request regular clinic or hospital visits to monitor the development of your child. Such visits may include blood tests and other tests.

In children whose mother took nucleoside and nucleotide analogues during pregnancy, the benefit from the reduced chance of being infected with HIV is greater than the risk of suffering from side effects.

Breast-feeding
Since the HIV virus passes into breast milk it is recommended that HIV-infected women taking Zidovudine in any form do ***not*** breast-feed their infants in order to avoid transmission of HIV.

Driving and using machines
No information on the effects of zidovudine on the ability to drive and use machines is available.

3. HOW TO TAKE ZIDOVUDINE CAPSULES

Always take Zidovudine Capsules exactly as your doctor or health care provider instructs you. You should check with your doctor, health care provider, or pharmacist if you are unsure how to use this medicine.

The usual dose of zidovudine (in any form) for adults and adolescents over 12 years of age is 600 mg a day taken in two divided doses of 300 mg each.

The usual dose of zidovudine (in any form) for children (6 weeks to <12 years of age) is based on weight (kg). Your doctor or health care provider will calculate the appropriate dose of Zidovudine Capsules for each child based on body weight.

Zidovudine Capsules in combination with other antiretroviral medication
Zidovudine Capsules will always be taken in combination with other antiretroviral medication. Make sure to follow the instructions within all supplied package leaflets.

If you take more Zidovudine Capsules than you should
If you take more Zidovudine Capsules than you should or if someone accidentally swallows some, there is no immediate danger. However, contact your doctor or health care provider, or the nearest hospital emergency department, for further advice as soon as you can after any accidental overdose.

If you forget to take Zidovudine Capsules
If you accidentally miss a dose, take your next normal dose when it is due. Do not take a double dose to make up for forgotten individual doses.

If you have further questions on the use of this product, ask your doctor, health care provider, or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zidovudine Capsules can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Zidovudine Capsules, those caused by any other medicines you may be taking at the same time, or by HIV disease. For this reason, it is important that you tell your doctor or health care provider of any change in your health.

Short-term adverse reactions to combination antiretroviral therapy are common. After you start taking Zidovudine Capsules, headache, insomnia, nausea and vomiting, abdominal pain (cramps), diarrhea, fatigue, and malaise may occur. These reactions are usually mild and disappear within a few weeks even if treatment is continued.

Common long-term adverse reactions include darkening of the skin. Rare and very rare long-term adverse reactions include a condition called lactic acidosis (see next paragraph), inflammation of the pancreas, fatty deposits in the liver, or failure of the liver.

Combination antiretroviral therapy may rarely cause a condition called lactic acidosis, a build-up of lactic acid in the body that can cause dehydration and coma. Deep, rapid breathing, drowsiness, and nonspecific symptoms such as nausea, vomiting, and stomach pain, may indicate the development of lactic acidosis.

Very commonly reported (greater than 1 in every 10 patients treated) side effects are headache, nausea, and changes in the distribution of body fat.

Commonly reported (greater than 1 in every 100 patients treated) side effects are vomiting, muscle aches, decreased red blood cells (anemia), decreased white blood cells (leukopenia, neutropenia), and transient increase of liver enzymes and bilirubin in the blood.

The following side effects are uncommon (between 1 in 1,000 and 1 in 100 patients treated): decreased number of blood platelets (thrombocytopenia), decreased white or red blood cells, and muscle disorders (myopathy).

There are rare reports (between 1 in 10,000 to 1 in 1,000 patients treated) of lactic acidosis, anxiety, depression, sleeplessness (insomnia), nail and skin pigmentation (increased or changed coloration), and increased urinary frequency.

There are very rare reports (less than 1 in 10,000 patients treated) of disruption of production of red blood cells (aplastic anemia).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These changes may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ("buffalo hump"). The cause and long-term health effects of these conditions are not known at this time.

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipemia (increased fats in the blood), and resistance to insulin.

If ypu experience any side effects, or if you notice any side effects not listed in this leaflet, tell your doctor, health care provider, or pharmacist as soon as possible.

5. STORING ZIDOVUDINE CAPSULES

Store at 20ºC to 25ºC (68ºF to 77ºF).

Do not use Zidovudine Capsules after the expiration (expiry) date, which is stated on the bottle or outer packaging or carton. The expiration (expiry) date refers to the last day of that month.

Do not use Zidovudine Capsules if you notice any visible signs of deterioration in the capsules or packaging.

Medicines should not be disposed of 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 contain
The active ingredient of Zidovudine Capsules is zidovudine. Each capsule contains 100 mg of zidovudine. Other inactive ingredients are microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, and magnesium stearate. The 100 mg empty hard gelatin capsule is printed with edible black ink that consists of black iron oxide, shellac. The capsule consists of titanium dioxide, sodium lauryl sulfate, and gelatin.

What Zidovudine Capsules looks like and contents of the packaging
Zidovudine Capsules are white hard gelatin capsules imprinted with “D” on the white cap and “01” on the white body.

For further information about this product, please contact the supplier:
Aurobindo Pharma, Ltd., Unit III, Survey No. 313, Bachupally, Quthubullapur, Hyderabad, Andhra Pradesh 500 072, India.

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zidovudine Capsules 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of zidovudine. Inactive ingredients: microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, and magnesium stearate. Capsule: size 3 white/white hard gelatin capsule (titanium dioxide, sodium lauryl sulfate, and gelatin) printed with edible black ink (black iron oxide, shellac).

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zidovudine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

4.2 Posology and method of administration

Zidovudine Capsules are for oral use.

Therapy should be prescribed by a physician experienced in the management of HIV-1 infection.

The usual dose of zidovudine in any form for adults and adolescents over 12 years of age is 600 mg a day taken in two divided doses of 300 mg each.

The usual dose of zidovudine in any form for children (6 weeks to <12 years of age) is based on weight (kg). Prescribers should calculate the appropriate dose of Zidovudine Capsules for each child based on body weight (kg). Never exceed the recommended adult dose. See Table below.

Redommended Pediatric Dosing for Zidovudine

Body Weight (kg)	Total Daily Dose	Twice daily (b.i.d.)	Three times a day (t.i.d.)
4 to < 9	24 mg/kg/day	12 mg/kg	8 mg/kg
≥ 9 to < 30	18 mg/kg/day	9 mg/kg	6 mg/kg
≥ 30	600 mg/day	300 mg	200 mg

Children should be assessed for the ability to swallow capsules or tablets. If a child is unable to reliably swallow a capsule or tablet, Zidovudine Oral Solution may be prescribed.

Zidovudine Capsules may be taken with or without food.

Dose Adjustments

Liver Disease: No dose adjustment is necessary for mild to moderate liver impairment but may be necessary for severe liver impairment.

Renal Impairment: No dose adjustment is necessary if creatinine clearance > 10 ml/min.

Hemodialysis Patients (adults): The recommended daily dose is 100 mg every 6 to 8 hours.

4.3 Contraindications

Zidovudine is contraindicated in patients with clinically significant hypersensitivity to zidovudine or to any of the components contained in the formulation.

Zidovudine is contraindicated in patients with abnormally low neutrophil counts (< 0.75 x 106/L) or low hemoglobin (< 7.5 g/dL or 4.7 mmol/L).

4.4 Special warnings and special precautions for use

- Zidovudine has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV disease.
- Prolonged use of zidovudine in any form has been associated with symptomatic myopathy.
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including zidovudine and other antiretrovirals. Discontinue treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur.

Transmission of HIV
Antiretroviral therapy has not been proven to lower risk of transmission or prevent transmission of HIV to others through sexual contact or contamination with blood.

Blood disease
Anemia, neutropenia, and leukopenia (usually secondary to neutropenia) can occur in patients receiving zidovudine. These conditions are dose dependent and usually occur after 4 to 6 weeks of therapy.

Discontinuation of zidovudine may be required if severe anemia (< 9 g/dL (5.6 mmol/L)) or myelosuppression (neutrophil count <1.0 x 109/L) occurs during treatment with zidovudine.

Liver disease
Caution should be exercised when administering an NRTI, including zidovudine, to any patient with liver disease.

Immune reconstitution inflammatory syndrome
In HIV-infected individuals with severe immunodeficiency when combination antiretroviral therapy is initiated, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Such reactions have typically been observed within the first few weeks or months of therapy. Relevant examples include cytomegalovirus retinitis, generalized and/or focal mycobacterium infections, and Pneumocystis jiroveci pneumonia. Any inflammatory symptoms should be evaluated and

treatment instituted when necessary. Optimal therapy has not been determined. Anti-inflammatory therapy may attenuate symptoms but many cases may resolve spontaneously.

Lipodystrophy and metabolic abnormalities
Combination antiretroviral therapy may lead to abnormal redistribution of body fat including central obesity, dorsocervical fat pad enlargement, peripheral and facial subcutaneous fat wasting (lipoatrophy), and breast enlargement.

Lactic acidosis
Lactic acidosis and hepatic steatosis are rare but severe complications associated with NRTI therapy that may occur after a few to several months of treatment. Lactic acidosis has a high mortality rate. Hyperlactatemia is defined as a venous lactate level > 2 mmol/L but false positive results due to faulty collection are common. If serum lactate is elevated, the test should be repeated with particular attention to patient rest and hydration. Patients with elevated serum lactate levels may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnea, fatigue, nausea, diarrhea, vomiting, and abdominal pain. Lactic acidosis may be associated with pancreatitis, liver failure, renal failure and motor paralysis. Risk factors other than use of NRTI include female gender and obesity.

Lactic acid levels < 5 mmol/L may not require treatment. Symptomatic patients usually have levels > 5 mmol/L and require discontinuation of all treatment including zidovudine. Lactic acid levels > 10 mmol/L usually are a medical emergency carrying a high risk of death. Seriously ill patients require supportive treatment, which may include intravenous hydration, mechanical ventilation, and/or dialysis. Recovery may be protracted.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are hematological disorders (anemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior).

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 national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

4.5 Interaction with other medicinal products and other forms of interaction

Stavudine and zidovudine compete for phosphorylation by the cellular enzyme thymidine kinase. Zidovudine in combination with stavudine is therefore not recommended.

Concurrent use of valproic acid, fluconazole, and probenecid increase exposure to zidovudine.

Zidovudine in combination with ribavirin is antagonistic *in vitro*. The concomitant use of ribavirin with zidovudine should be avoided if possible.

Concomitant treatment with potentially nephrotoxic or myelosuppressive agents (e.g., systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, cidofovir, ganciclovir, valganciclovir, interferon, vincristine, vinblastine, and doxorubicin) may increase the risk of adverse reactions to zidovudine. If concomitant therapy with zidovudine and any of these medicinal products is necessary then extra care must be taken in monitoring renal function and hematological parameters and, if required, the dosage of one or more agents should be reduced.

Zidovudine is not metabolized via the CYP450 pathway.

4.6 Pregnancy and lactation

Pregnancy: Zidovudine is assigned FDA Pregnancy Category C status (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). No increased risk of birth defects have been reported for zidovudine (www.apregistry.com).

Nursing Mothers: Zidovudine is excreted into the breast milk of lactating mothers. Because of the potential for HIV transmission and adverse effects caused by zidovudine in nursing infants, HIV-infected mothers should be instructed not to breast-feed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Short-term adverse reactions to combination antiretroviral therapy are common. Headache, insomnia, nausea and vomiting, abdominal pain or cramps, diarrhea, fatigue, and malaise may occur with initiation of treatment. These reactions are usually mild and disappear within a few weeks even if treatment is continued.

Common long-term adverse reactions include hyperpigmentation. Rare and very rare long-term adverse reactions include lactic acidosis, hepatic steatosis, pancreatitis, liver failure, and muscle toxicity.

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV-1 infection with zidovudine.

The adverse events considered at least possibly related to zidovudine treatment are listed below by body system, organ class, and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), and very rare (<1/10,000).

Blood and lymphatic systems disorders
Common: anemia, leukopenia, neutropenia
Uncommon: thrombocytopenia, pancytopenia
Rare: pure red cell anemia
Very rare: aplastic anemia

Metabolic and nutrition disorders
Very common: changes in distribution of body fat
Rare: lactic acidosis

Psychiatric disorders
Rare: anxiety and/or depression

Nervous system disorders
Very common: Headache
Rare: Insomnia

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting

Hepatobiliary disorders
Common: Transient elevation of liver enzymes and bilirubin

Skin and subcutaneous tissue disorders
Rare: nail and skin pigmentation, urticaria and sweating

Musculoskeletal and connective tissue disorders
Common: myalgia
Uncommon: myopathy

Renal and urinary disorders
Rare: urinary frequency

4.9 Overdose

Acute overdoses of zidovudine have been reported involving exposures up to 50 grams. No specific symptoms or signs were identified following overdosage apart from those listed above as adverse events. All involved individuals recovered without permanent sequelae.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiretroviral, ATC code: J05AF01

Zidovudine is a thymidine dideoxynucleoside analogue that has activity against human immunodeficiency virus 1 and 2. Zidovudine is phosphorylated by thymidine kinase to the active metabolite zidovudine 5'-triphosphate and its main mode of action is as a chain terminator of viral reverse transcription.

In addition to the inhibitory effect on HIV reverse transcriptase, zidovudine 5'-triphosphate inhibits cellular DNA polymerase beta and gamma and has been shown to be able to reduce the synthesis of mitochondrial DNA.

Clinical efficacy
Zidovudine has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs. These studies demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with other nucleoside analogues and either a NNRTI analogue or a PI. In recent studies by intention-to-treat analysis > 75% of subjects have plasma HIV RNA <50 copies/mL after 48 weeks of combination antiretroviral treatment.

Isolates with thymidine-analogue associated mutations caused by the thymidine-analogues, zidovudine and stavudine, at positions M41L, K65R, D67N, K70R, L210W, T215Y/F, and K219Q/E in the reverse transcriptase gene have reduced susceptibility to nucleoside analogues including zidovudine (www.iasusa.org).

Patients who are infected with known zidovudine- or stavudine-resistant HIV or patients who have previously experienced virological failure on a zidovudine- or stavudine-containing regimen may not respond sufficiently to further treatment with a combination regimen containing zidovudine.

5.2 Pharmacokinetic properties

Absorption and Bioavailability
Zidovudine is well absorbed following oral administration. Bioavailability is between 60 and 70%. Peak plasma concentrations occur within 1 hour after dosing. In healthy volunteers, at a therapeutic dose of 300 mg twice daily, mean steady-state Cmax of zidovudine in plasma was 2 µg/mL. The mean area under the curve (AUC) over a dosing interval of 12 hours was 2.4 µg.h/mL.

Distribution
The estimated volume of distribution is 1.6 L/kg. Protein binding is 34-38%.

Metabolism / Elimination
The observed half-life is 1 hour. The mean systemic clearance of zidovudine is approximately 1.6 L/h/kg. 90% of zidovudine and its major metabolite, 5' glucuronylzidovudine, are excreted in urine.

5.3 Preclinical safety data

Administration of high doses of zidovudine in animal toxicity studies was not associated with any major organ toxicity. The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, magnesium stearate; black iron oxide, shellac (ink on capsule); titanium dioxide, sodium lauryl sulfate, and gelatin (capsule)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 20ºC to 25ºC (68ºF to 77ºF)

6.5 Nature and contents of container

Plastic bottles and 10 x 10 unit-dose packages containing white/white hard gelatin capsules imprinted with “D” on the white cap and “01” on the white body

6.6 Instructions for use and handling and disposal

No special requirements

7. Supplier

Aurobindo Pharma, Ltd., Unit III, Survey No. 313, Bachupally, Quthubullapur, Hyderabad, Andhra Pradesh, India 500 072

8. DATE OF USFDA APPROVAL

March 27, 2006

LABELING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Zidovudine Capsules 100 mg

1. NAME OF THE MEDICINAL PRODUCT

Zidovudine Capsules 100 mg

2. STATEMENT OF ACTIVE SUBSTANCES

Each capsule contains 100 mg of zidovudine

3. LIST OF EXCIPIENTS

Microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, magnesium stearate; black iron oxide, shellac (ink on capsule); titanium dioxide, sodium lauryl sulfate, and gelatin (capsule)

4. PHARMACEUTICAL FORM AND CONTENTS

Capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN

Keep out of reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use

8. EXPIRATION DATE

<EXP MM/YYYY>

9. SPECIAL STORAGE CONDITIONS

Store at 20ºC to 25ºC (68ºF to 77ºF)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF SUPPLIER

Aurobindo Pharma, Ltd., Unit III, Survey No. 313, Bachupally, Quthubullapur, Hyderabad, Andhra Pradesh, India 500 072

12. MANUFACTURER'S BATCH NUMBER

<Batch> <Lot> <number>

13. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

14. INSTRUCTIONS FOR USE

SCIENTIFIC DISCUSSION

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	Zidovudine Capsules
Supplier	Aurobindo Pharma, Ltd.
Active Pharmaceutical Ingredient (API)	Zidovudine
International Nonproprietary Name	Zidovudine
Pharmaco-therapeutic group (ATC Code)	Antiviral for systemic use—nucleoside reverse transcriptase inhibitor (J05AF01
Therapeutic indication	Zidovudine Capsules are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents

1. Introduction

Zidovudine Capsules are indicated for the treatment of Human Immunodeficiency Virus (HIV-1) infection in combination with other antiretroviral agents. Zidovudine Capsules is not indicated for use in patients with clinically significant hypersensitivity to zidovudine or any of the components contained in the formulation.

It is recommended that therapy be initiated only on the advice of a physician or healthcare professional experienced in the diagnosis and management of HIV infection and related disease.

2. Assessment of Quality

Introduction
The assessment was conducted by the USFDA as an abbreviated new drug application (ANDA) reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR).

Composition
Each capsule contains 100 mg of zidovudine. Other inactive ingredients: microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, and magnesium stearate. The 100 mg empty hard gelatin capsule is printed with edible black ink consisting of black iron oxide and shellac. The capsule consists of titanium dioxide, sodium lauryl sulfate, and gelatin. Zidovudine Capsules are white/white size 3 hard gelatin capsules imprinted with "D" on the white cap and "01" on the white body.

Control of active pharmaceutical ingredient (API)
Zidovudine Capsules controls are consistent with cGMP and USP requirements and take into account product- and process-specific needs and information.

Control testing of the finished medicinal product
The release and shelf-life specifications are consistent with the requirements of major internationally used pharmacopoeias and guidelines for capsules. The test methods have been adequately validated.

Stability
Stability studies have been conducted and results show that the products conform with the proposed end of shelf life specification including description, disintegration time, dissolution, assay, and degradation products. Stability data for this product in the proposed marketing containers conforms to specifications. Based on the stability data provided the proposed expiration dating is acceptable.

Conclusions
It is concluded that the data submitted ensure acceptable quality of the finished medicinal product when stored under the conditions specified on the label.

3. Assessment of Bioequivalence

The USFDA Office of Generic Drugs Division of Bioequivalence reviewed data submitted in a review of two (fasting and fed) *in vivo* bioequivalence (BE) studies. This application

referenced Retrovir® Capsules 100mg (GlaxoSmithKline). The two-way crossover BE studies compared the 100 mg capsules of the test and reference products in healthy adult males (fasting: n = 36 and fed: n = 37). Dissolution testing was acceptable. The BE application was deemed acceptable by the USFDA Office of Generic Drugs Division of Bioequivalence.

4. Summary of Product Safety and Efficacy

4.1 Introduction

Background
Zidovudine Capsules 100 mg have been shown to conform to the same appropriate standards of quality, efficacy, and safety as those required of the innovator`s product. According to the submitted data on quality and bioavailability Zidovudine Capsules 100 mg are pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Retrovir® Capsules 100 mg, for which benefits have been proven in terms of virological and immunological efficacy.

Product Design
The development strategy for Zidovudine Capsules was concentrated on compatibility of the active ingredient zidovudine with the excipients identified to match the dissolution profile of the innovator, thus producing a robust formulation.

Clinical Safety
The clinical safety of this product is considered to be acceptable when the guidances and restrictions presented in the Summary of Product Characteristics (SPC), Part 4 of this Public Assessment Report, are taken into consideration. Clinical efficacy of Zidovudine Capsules is discussed in Section 5.1 (“Pharmacodynamic Properties”) in the SPC. Clinical safety is discussed in Section 5.3 (“Pre-clinical Safety”) in the SPC. Also see Section 4 of the SPC (“Clinical Particulars”) for discussion of contraindications, special precautions, interactions, use in pregnancy, patient exposure (including overdosage), interactions, and adverse events.

Approved Indication
Zidovudine Capsules are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

Clinical Pharmacology

Pharmacodynamics

Zidovudine is a thymidine dideoxynucleoside analogue. It is phosphorylated by thymidine kinase to the active metabolite zidovudine 5’-triphosphate. Zidovudine shows antiretroviral activity *in vitro* against human immunodeficiency virus type I (HIV-1) and HIV-2.

See the Summary of Product Characteristics, Part 4 of this Public Assessment Report, Section 5.1, for a more extensive discussion of pharmocodynamic properties of zidovudine.

Pharmacokinetics

Absorption and Bioavailability: Zidovudine is well absorbed following oral administration. Bioavailability is between 60 and 70%.

Distribution: The estimated volume of distribution is 1.6 l/kg. Protein binding is 34-38%.

Metabolism / Elimination: The observed half-life is 1 hour. The mean systemic clearance of zidovudine is approximately 1.6 l/h/kg. 90% of zidovudine and its major metabolite, 5' glucuronylzidovudine, are excreted in urine.

Drug Interactions, related side effects and contraindications

Zidovudine Capsules are contraindicated in patients with clinically significant hypersensitivity to zidovudine or to any of the components contained in the formulation.

Zidovudine is contraindicated in patients with abnormally low neutrophil counts (< 0.75 x 106/l) or low hemoglobin (< 7.5 g/dl or 4.7 mmol/l).

Stavudine and zidovudine compete for phosphorylation by the cellular enzyme, thymidine kinase, and zidovudine is therefore not recommended in combination with stavudine.

Valproic acid, fluconazole, and probenecid increase exposure to zidovudine.

Zidovudine in combination with ribavirin is antagonistic *in vitro*. Avoid concomitant use of ribavirin with zidovudine if possible.

Concomitant treatment with potentially nephrotoxic or myelosuppressive drugs (e.g., systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, cidofovir, ganciclovir, valganciclovir, interferon, vincristine, vinblastine, and doxorubicin) may increase the risk of adverse reactions to zidovudine. If concomitant use of zidovudine and any of these drugs is necessary then extra care must be taken in monitoring renal function and hematological parameters. If required, the dosage of one or more agents should be reduced.

Zidovudine is not metabolized via the CYP450 pathway.

Clinical Efficacy

See the Summary of Product Characteristics, Part 4 of this Public Assessment Report, Section 5 ("Pharmacological Properties"), for discussion of clinical efficacy.

Clinical studies in special populations

Liver Disease
No dose adjustment is necessary for mild to moderate liver impairment but may be necessary for severe liver impairment.

Renal Impairment
No dose adjustment is necessary if creatinine clearance > 10 ml/min.

Hemodialysis Patients
The recommended daily dose is 100 mg every 6 to 8 hours

Clinical Safety

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV infection with zidovudine. The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), and very rare (<1/10,000).

Blood and lymphatic systems disorders
Common: Anemia, leukopenia, and neutropenia
Uncommon: Thrombocytopenia and pancytopenia
Rare: Pure red cell anemia
Very rare: Aplastic anemia

Metabolic and nutrition disorders:
Very common: Changes in body fat distribution
Rare: lactic acidosis

Psychiatric disorders
Rare: Anxiety and depression

Nervous system disorders
Very common: Headache
Rare: Insomnia

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting

Hepatobiliary disorders
Common: Transient elevation of liver enzymes and bilirubin

Skin and subcutaneous tissue disorders
Rare: Nail and skin pigmentation

Musculoskeletal and connective tissue disorders:
Common: Myalgia
Uncommon: Myopathy

Renal and urinary disorders
Rare: Urinary frequency

5. Overall Conclusion and benefit risk assessment

Quality
The quality of Zidovudine Capsules is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics (Part 4 of this Public

Assessment Report). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence
Zidovudine Capsules 100 mg have been shown to be bioequivalent to Retrovir® capsules 100 mg.

Clinical Efficacy and Safety
Zidovudine Capsules 100 mg are considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics (Part 4 of this Public Assessment Report) are taken into consideration.

Benefit risk assessment
Based on USFDA assessment of data on quality, bioequivalence, safety, and efficacy, the benefit risk profile of Zidovudine Capsules 100 mg was considered acceptable for the following indication: HIV-1 infection in combination with other antiretroviral agents.

Products added to the WHO prequalification list on the basis of USFDA approval rely on scientific assessment and inspections conducted by the USFDA. A product listed as USFDA **approved** indicates that the product meets all of USFDA's safety, efficacy, and manufacturing quality standards, and is eligible for purchase with PEPFAR funds.

For further information about this medicinal product, please contact:
Justina A. Molzon, M.S. Pharm, J.D.
Associate Director for International Programs
U. S. Food and Drug Administration
Center for Drug Evaluation and Research
Building 51, Room 6118
10903 New Hampshire Ave.
Silver Spring, MD 20993 USA
justina.molzon@fda.hhs.gov