1.3 PRESCRIBING INFORMATION

1.3.1 Summary of Product Characteristics

Enclosed overleaf.

SUMMARY OF PRODUCT CHARACTERISTICS

ZIDOVUDINE TABLETS USP 300 mg

$R_{X\ Only}$

1 NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Zidovudine Tablets USP 300 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Zidovudine USP 300 mg

Excipients: Microcrystalline cellulose, hypromellose, sodium starch glycolate, magnesium stearate, titanium dioxide and polyethylene glycol.

3 PHARMACEUTICAL FORM

Film coated Tablets.

Zidovudine Tablets are White coloured, biconvex, round film coated tablets debossed with 'D' on one side and '11' on other side.

The tablets should not be divided.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zidovudine Tablets USP 300 mg is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in patients weighing 25 kg or more.

Zidovudine Tablets USP 300 mg is also indicated for the use in pregnant women for prevention of maternal-fetal HIV-1 transmission (see section 4.2)

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

4.2 Posology and method of administration

Oral use

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

Patients weighing 25 kg or more: the recommended dose of zidovudine is 300 mg twice daily. Zidovudine may be taken with or without food.

Dosage in the prevention of maternal-foetal transmission

It is recommended that the most recent official treatment guidelines (e.g. those issued by WHO) should be consulted for information regarding dosing for this indication.

Other formulations containing less zidovudine are available for dosing in children less than 25kg.

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. Zidovudine Tablets USP 300 mg dose reduction or interruption should be considered in the absence of alternative treatments (see sections 4.3 and 4.4).

Liver Disease

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

Renal Impairment

In patients with severe renal failure (CrCl <10 ml/min), with or without haemodialysis, the dose should be reduced to 300-400 mg/day.

Elderly

Special care is advised in this age group due to age-associated changes such as the decrease in renal function and alteration of haematological parameters.

4.3 Contraindications:

Zidovudine Tablets USP 300 mg is contraindicated in patients with clinically significant hypersensitivity to zidovudine or to any of the excipients.

Zidovudine Tablets USP 300 mg is contraindicated in patients with abnormally low neutrophil counts (< 0.75 x 10^6/l) or low haemoglobin (< 7.5 g/dl or 4.7 mmol/l).

Zidovudine Tablets USP 300 mg is contraindicated 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

Transmission of HIV

Antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Patients should continue to take appropriate precautions.

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

Haematological Adverse Reactions:

Anaemia, neutropenia and leucopoenia (usually secondary to neutropenia) can occur in patients receiving zidovudine. These are dose dependent and usually occur after 4 to 6 weeks of therapy.

Discontinuation of zidovudine may be required if severe anaemia (< 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 NRTIs, including zidovudine, to any patient with liver disease.

Immune Reactivation Syndrome

In HIV-infected patients with pre-existing severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary.

Lipodystrophy

Combination antiretroviral therapy has been associated with a redistribution of body fat (lipodystrophy) in HIV patients. A higher risk of peripheral fat loss has been associated with stavudine or zidovudine use, and also with e.g. older age of the patient, longer duration of ART and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8). Lipid disorders should be managed appropriately, including the substitution of zidovudine by an alternative antiretroviral agent, if feasible (see section 4.8).

Lactic acidosis

Lactic acidosis is a rare but severe, potentially life-threatening complication associated with NRTI use. It may occur after a few to several months of treatment. Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI- related lactic acidosis include female gender and obesity. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l

and require discontinuation of all NRTIs, including zidovudine. Lactic acid levels > 10 mmol/l usually are a medical emergency.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia), metabolic isorders (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 national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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:

Zidovudine does not inhibit the cytochrome P450 isoform CYP3A and is not metabolized by CYP450 enzymes. Therefore the risk of drug interactions through this mechanism is low.

Since zidovudine and stavudine act antagonistically in vitro, Zidovudine Tablets USP 300 mg should not be used concomitantly with stavudine.

Co-administration of zidovudine with ribavirin leads to additive or synergistic bone marrow toxicity. For this reason, zidovudine should be replaced by an alternative antiretroviral agent in patients treated with ribavirin.

Co-administration of zidovudine with rifampicin decreases the exposure to zidovudine. However, the clinical significance of this is unknown. Dose modifications of zidovudine in this situation have not been formally evaluated.

Probenecid, valproic acid and fluconazole increase the exposure to zidovudine. Patients should be closely monitored for haematological toxicity.

Clarithromycin tablets reduce the absorption of zidovudine. The clinical relevance is unclear. However, this effect can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.

Atovaquone and methadone have been shown to increase exposure to zidovudine. The clinical relevance is unknown.

Phenytoin plasma levels have been reported to be altered in either way in patients receiving zidovudine. Thus, phenytoin levels should be carefully monitored in patients receiving Zidovudine Tablets USP 300 mg and phenytoin.

Concomitant treatment with therapeutic doses of dapsone (which may cause haemolytic anaemia), of potentially nephrotoxic or myelosuppressive agents (e.g. systemic pentamidine, pyrimethamine, cotrimoxazole, 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 dose of the concomitantly administered drug should be reduced.

Clinical data do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole, aerosolized pentamidine, pyrimethamine, dapsone and aciclovir at the doses used in prophylaxis of opportunistic infections.

4.6 Pregnancy and lactation

Pregnancy

No increased risk of birth defects have been reported for zidovudine.

However, risks to the fetus cannot be ruled out.

Breastfeeding

Zidovudine is excreted into the breast milk of lactating mothers. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter.

Preferred options may vary depending on the local circumstances.

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.

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. The clinical status of the patient and the adverse reaction profile of Zidovudine Tablets USP 300 mg should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

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 with advanced HIV disease, particularly in patients with CD4 cell counts less than 100/mm3. Dosage reduction or cessation of therapy may become necessary (see section 4.4). Also, zidovudine has been associated with the lipodystrophy syndrome, including peripheral fat loss (see section 4.4.). The adverse reaction profile appears similar for adults and children.

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 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), very rare (<1/10,000), or not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Common: Anaemia, neutropenia and leucopenia.

Uncommon: Thrombocytopenia and pancytopenia with marrow hypoplasia

Rare: Pure red cell aplasia

Very rare: Aplastic anaemia

Metabolism and nutrition disorders

Rare: Anorexia and lactic acidosis in the absence of hypoxaemia

Psychiatric disorders
Rare: anxiety and depression

Nervous system disorders:
Very common: headache
Rare: insomnia.

Gastrointestinal disorders
Very common: nausea
Common: vomiting

Hepatobiliary disorders
Common: transient elevation of liver enzymes and bilirubin
Rare: severe hepatomegaly with steatosis

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

Musculoskeletal and connective tissue disorders
Common: myalgia
Uncommon: myopathy
Not known: osteonecrosis (see section 4.4).

General disorders and administration site conditions
Not known: immune reconstitution syndrome.

Renal and urinary disorders
Rare: urinary frequency increased.

Adverse reactions with zidovudine for the prevention of maternal-foetal transmission: Haemoglobin concentrations in infants directly exposed to zidovudine for six weeks post partum 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.

4.9 Overdose

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

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: Antiretroviral, ATC code: J05AF01

Zidovudine is a thymidine dideoxynucleoside analogue that has activity against HIV-1 and HIV-2. Zidovudine is phosphorylated by thymidine kinase to the active metabolite zidovudine 5'-triphosphate. Its mechanism 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 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 have demonstrated significant decreases in plasma HIV RNA and increases in CD4 cell counts when used in combination with another NRTI and either a NNRTI or a PI. In recent studies in treatment-naïve patients infected with HIV-1, by intention-to-treat analysis > 75% of subjects have plasma HIV RNA < 50 copies/ml after 48 weeks of combination antiretroviral treatment including zidovudine.

On virological failure, resistance to zidovudine is developed along two separate, though not mutually exclusive, pathways. The first of these include M41L, L210W and T215F/Y. The second includes D67N, K70R and K219E/Q. Collectively these mutations are termed "thymidine analog mutations" (TAM). In viruses with M184V, two to three TAMs are generally required for phenotypically detectable and clinically significant zidovudine resistance. M41L, L210W, and T215Y have a greater effect on zidovudine susceptibility and cross-resistance to other NRTIs than the other TAMs. Other important mutations selected for by zidovudine include T69 insertion mutations and the Q151M complex, where this mutation appears in combination with mutations at positions 75, 77, and 116. Both of these patterns

confer high- level resistance to zidovudine and all other presently available NRTIs. The likelihood of a gradual accumulation of mutations conferring resistance to the entire class of NRTI, upon virological failure with combination therapy including zidovudine, underscores the importance of early detection of virological failure. Delayed detection of virological failure may severely limit the options for second line therapy.

In the US ACTG 076 trial, zidovudine reduced the rate of maternal-foetal transmission of HIV-1 (23% infection rate for placebo versus 8% for zidovudine) when HIV-positive pregnant women (14 to 34 weeks gestation) were given 100 mg five times a day and their newborn infants were given 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).

5.2 Pharmacokinetic properties

Pharmacokinetic properties

Absorption and bioavailability

Zidovudine is well absorbed from the gastrointestinal tract, with a bioavailability of 60 – 70%.

As Zidovudine Tablets USP 300 mg met the WHO criteria for a BCS based biowaiver a bioequivalence study was not conducted. Therefore, no pharmacokinetic data are available for this product.

From a bioequivalence study conducted with the innovator product the following data are reported: 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 2.29 µg/ml (54%), 0.02µg/ml(96%), and 2.24 h*µg/ml, respectively.

Distribution

The mean apparent volume of distribution of zidovudine is 1.6 l/kg. Plasma protein binding is 34% to 38%.

Metabolism
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 has been identified as a metabolite of zidovudine following intravenous dosing.

Elimination
In studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 l/h/kg. The half-life of intracellular zidovudine triphosphate has been estimated to around 7 hours. Renal clearance of zidovudine is estimated to be 0.34 l/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys.

Zidovudine concentrations are increased in patients with advanced renal failure.

5.3 Preclinical safety data
Administration of zidovudine in animal toxicity studies at high doses 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, hypromellose, sodium starch glycolate, magnesium stearate, titanium dioxide and polyethylene glycol.

6.2 Incompatibilities
None

6.3 Shelf-life
Please refer outer package for expiry date.

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container
Container containing 60 tablets each.

6.6 Instructions for use and handling
No special requirements.

7 MARKETING AUTHORIZATION HOLDER:

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