WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA483 product name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg zidovudine.

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets.

Zidovudine Tablets USP 300 mg are white, round biconvex, film-coated tablets plain on both sides.

The tablets should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA483 product name] is indicated as part of antiretroviral combination therapy for the treatment of HIV-1 infection in patients weighing 25 kg or more.

[HA483 product name] is also indicated for the use in pregnant women for prevention of maternal-fetal HIV-1 transmission.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Oral use.

Antiretroviral therapy should be prescribed by a health care provider experienced in the management of HIV infection.

Posology

Treatment of HIV infection

The recommended dose of zidovudine for patients weighing 25 kg or more is 300 mg twice daily.

Prevention of mother-to-child transmission

The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted for information prevention of mother-to-child transmission.

Zidovudine formulations suitable for children and adolescents weighing less than 25 kg are available.

Dosage adjustments

Patients with haematological adverse reactions

Substitution of zidovudine should be considered in patients whose haemoglobin levels or neutrophil counts fall in a clinically significant way. Other potential causes of anaemia or neutropenia should be ruled out.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Zidovudine 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

Zidovudine dose should be reduced in patients with severe renal failure (creatinine clearance less than 10 mL/minute), even in patients on haemodialysis, to 300–400 mg daily

Elderly

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

Missed dose

If the patient forgets to take a dose and:

- if it is more than 2 hours to the next dose, the patient should take the dose immediately and take the next dose at the usual time
- if it is less than 2 hours to the next dose, the patient should skip the dose and take the next dose at the usual time

The patient should not take a double dose to make up for a forgotten dose.

Method of administration

[HA483 product name] can be taken with food or between meals.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

[HA483 product name] must **not** be used in patients with:

- abnormally low neutrophil count (less than 0.75×10^9/L),
- abnormally low haemoglobin (less than 75 g/L or 4.65 mmol/L).

Zidovudine is contraindicated in newborn infants with hyperbilirubinaemia requiring treatment other than phototherapy, or with transaminase levels of over 5 times the upper limit of normal.

4.4 Special warnings and precautions for use

Opportunistic infections

Health care providers should tell patients with impaired immunity that opportunistic infections or other complications of HIV infection may still develop while receiving antiretroviral medicines. This risk reduces as the immune system recovers.

Haematological adverse reactions

Anaemia, neutropenia and leucopenia can occur in patients receiving zidovudine, especially in patients with advanced HIV disease or poor bone-marrow reserve or with vitamin B12 deficiency, and usually after at least 4–6 weeks of therapy.

Therefore, haematological parameters should be monitored in patients receiving [HA483 product name] with the following suggested frequency:

- in advanced HIV disease, at least every 2 weeks during the first 3 months of therapy, and monthly thereafter.
- in early (non-symptomatic) HIV disease, every 1–3 months according to the patient's overall condition.

Zidovudine may need to be interrupted, discontinued or its dose reduced if severe anaemia (less than 90 g/L (5.6 mmol/L)) or myelosuppression (neutrophil count less than 1.0×10^9/L) occurs during treatment with zidovudine.

Liver disease

Nucleoside reverse transcriptase inhibitors (NRTIs), including zidovudine, should be used with caution in any patient with liver disease.

Patients with liver dysfunction, including chronic active hepatitis, have an increased frequency of liver 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.

Patients with chronic hepatitis B or C who are treated with combination antiretroviral therapy, have an increased risk of severe and potentially fatal hepatic adverse events.

In the case of concomitant antiviral therapy for hepatitis B or C, the relevant product information for these medicines should be consulted. Concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

Lactic acidosis

Lactic acidosis usually associated with hepatomegaly and hepatic steatosis has been reported with the use of zidovudine. It generally occurred after a few months of treatment. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid 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.

Treatment with zidovudine should be discontinued if there is symptomatic hyperlactataemia and metabolic or lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Zidovudine should be given with caution to any patient (particularly obese women) with hepatomegaly, hepatitis or other risk factors for liver disease and hepatic steatosis (including certain medicines and alcohol). Patients co-infected with hepatitis C and treated with interferon alfa and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Immune reactivation syndrome

Immune reactivation syndrome has been reported in patients treated with combination antiretroviral therapy. During early stages of treatment, patients whose immune system responds to antiretroviral therapy may develop an inflammatory response to slow-developing or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus retinitis, Pneumocystis jirovecii pneumonia, or tuberculosis). These reactions may require further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, autoimmune hepatitis, polymyositis, and Guillain-Barré syndrome) have also been reported in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after starting antiretroviral treatment.

Lipoatrophy

Treatment with zidovudine is associated with loss of subcutaneous fat, which has been linked to mitochondrial toxicity. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs and buttocks, may not be reversible when switching to a zidovudine-free regimen. Patients should be regularly assessed for lipoatrophy during therapy with zidovudine. Therapy should be switched to an alternative regimen if lipoatrophy is suspected.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is some evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. HIV treatment guidelines should be used for recommendations on monitoring blood lipids and glucose. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following uterine exposure

Nucleoside and nucleotide analogues can cause mitochondrial damage. Mitochondrial dysfunction has been reported in HIV-negative infants exposed to nucleoside analogues in the uterus or postnatally. The main adverse reactions are haematological disorders (anaemia and neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These reactions are often transient. Some late-onset neurological disorders have been reported (hypertonia, convulsion and abnormal behaviour). It is not known if the neurological disorders are transient or permanent. These findings should be considered for any child exposed in the uterus to nucleoside and nucleotide analogues who has severe features of unknown aetiology, particularly neurological effects

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with advanced HIV disease or long-term combination antiretroviral therapy. Aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Other drugs

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

4.5 Interaction with other medicinal products and other forms of interaction

Zidovudine is primarily eliminated by hepatic conjugation by UGT enzymes, to form an inactive glucuronide metabolite. Therefore, co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine exposure.

Zidovudine is not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and it does not inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicines metabolised by major P450 enzymes.

The following list of interactions is not exhaustive but is representative of the classes of medicines where caution should be exercised.

[HA483 product name] interactions

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
HIV antiretrovirals		
Stavudine with zidovudine	In vitro antagonism of antiretroviral activity could result in decreased efficacy of both drugs.	Stavudine should not be co-administered with [HA483 product name].
Lamivudine with zidovudine	Zidovudine C_{max} ↑ 28% Zidovudine AUC ↔	No overall effect on pharmacokinetics
Other antivirals		
Ribavirin with zidovudine	Exacerbation of anaemia has been reported in patients receiving ribavirin and zidovudine.	Ribavirin and zidovudine should not be co-administered, particularly in patients with zidovudine-induced anaemia.
Anti-infectives		
Albendazole with zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Clarithromycin with zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓ 12%	Administration of [HA483 product name] and clarithromycin should be separated by at least 2 hours.
Sulfadiazine with zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Vancomycin with zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Antifungal		
Fluconazole with zidovudine (400 mg once daily/200 mg three times daily)	Zidovudine AUC ↑ 74% (UGT inhibition)	Co-administration may increase zidovudine exposure. Routine dose modification is not warranted; however, the patient should be monitored for zidovudine toxicity.
Antimalarial		
Amodiaquine and zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Primaquine and zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Atovaquone and zidovudine	Zidovudine AUC ↑ 33%	Acute therapy unlikely to have adverse reactions however should be monitored with prolonged atovaquone
Antimycobacterial		
Rifampicin and zidovudine (600 mg daily/200 mg three times daily)	Zidovudine AUC ↓ 48% ± 34%. Loss of efficacy	The concomitant use of rifampicin with zidovudine should be avoided

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Antipsychotics		
Fluphenazine with zidovudine	Potential haematological toxicity.	Haematological parameters should be monitored
Quetiapine with zidovudine		
Antiepileptics		
Phenobarbital with zidovudine	Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction.	Response to antiretroviral therapy should be monitored. Insufficient data to recommend dosage adjustment.
Phenytoin with zidovudine	Phenytoin AUC ↓	Phenytoin concentration should be monitored. Need for dosage adjustment unlikely
Valproic acid with zidovudine (250 mg or 500 mg three times daily/100 mg three times daily)	Zidovudine AUC ↑ 80% (UGT inhibition)	Patient should be monitored for signs of zidovudine toxicity (section 4.8).
Cytotoxics		
Carboplatin with zidovudine	Potential renal and haematological toxicity	Renal function and haematological parameters should be monitored and dose reduction should be considered.
Chlorambucil with zidovudine Cisplatin with zidovudine Cyclophosphamide with zidovudine Cytarabine with zidovudine Dacarbazine with zidovudine Daunorubicin with zidovudine Docetaxel with zidovudine Fluorouracil with zidovudine Gemcitabine with zidovudine Ifosfamide with zidovudine Imatinib with zidovudine Mercaptopurine with zidovudine Methotrexate with zidovudine Oxaliplatin with zidovudine Paclitaxel with zidovudine	Potential haematological toxicity	Haematological parameters should be monitored

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Opioids		
Methadone with zidovudine (30–90 mg once daily/200 mg every 4 hours)	Zidovudine AUC ↑ 43% Methadone AUC ↔	The clinical significance is not known. Monitor for signs of zidovudine toxicity. Methadone dosage adjustment may be required occasionally.
Uricosuric		
Probenecid with zidovudine (500 mg four times daily/2 mg/kg three times daily)	Zidovudine AUC ↑ 106% (UGT inhibition)	The clinical significance is not known. The patient should be monitored for signs of haematological toxicity.
Miscellaneous		
Methyldopa with zidovudine	Potential haematological toxicity.	Haematological parameters should be monitored

↓	Decreased	AUC	area under the curve (bioavailability)
↑	Increased	C_{max}	maximum (peak) concentration (in plasma or blood)
↔	No change	C_{min}	minimum (trough) concentration (in plasma or blood)

Nephrotoxic and myelosuppressive drugs

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive drugs (e.g. systemic pentamidine, dapsone, pyrimethamine, sulfamethoxazole + trimethoprim, 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.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

No increased risk of birth defects has been reported for zidovudine. A large amount of cumulative information on pregnant women taking zidovudine indicate that malformation is unlikely.

The use in pregnant women of zidovudine alone, with subsequent treatment of the newborn infants, can reduce the rate of maternal-fetal transmission of HIV-infection.

Placental transfer of zidovudine occurs in humans. Zidovudine can be used during pregnancy if clinically needed.

A variable degree of mitochondrial damage may occur with the use of nucleoside and nucleoside analogues. There are reports of mitochondrial dysfunction in HIV-negative infants exposed in the uterus or postnatally to nucleoside analogues.

Zidovudine has been associated with reproductive toxicity findings in animal studies (see section 5.3).

Breastfeeding

Zidovudine is present in breast milk at concentrations similar to those in the serum. Current recommendations on HIV and breast-feeding (e.g. those from the WHO) should be consulted to advise patients on this matter. Preferred options may vary depending on the local circumstances

Fertility

Zidovudine did not impair male or female fertility in rats. 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

[HA483 product name] is not expected to affect the patient's ability to drive or use machines. However, the patient's clinical status and individual experience of adverse effects (e.g. fatigue) should be borne in mind to determine if the patient can safely perform skilled tasks.

4.8 Undesirable effects

[HA483 product name] contains zidovudine and adverse reactions associated with this active substance may be expected. The most serious adverse reactions include anaemia (which may require transfusions), neutropenia and leukopenia. These occurred more frequently at higher doses (1.2–1.5 g/day) and with advanced HIV disease, particularly in patients with CD4 cell counts less than 100/mL. Dosage reduction or cessation of therapy may become necessary (see section 4.4).

Zidovudine has been associated with lipodystrophy syndrome, including peripheral fat loss (see section 4.4.).

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

The undesirable effects of [HA483 product name] are listed below. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from the available data).

Blood and lymphatic systems disorders

Common	anaemia, neutropenia, leucopenia
Uncommon	thrombocytopenia, pancytopenia
Rare	pure red cell aplasia
Very rare	aplastic anaemia

Metabolic and nutrition disorders

Rare	lactic acidosis, anorexia
Frequency not known	lipoatrophy, weight increase, hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia,

Psychiatric disorders

Rare	anxiety, depression

Nervous system disorders

Very common	headache
Common	dizziness
Rare	insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions

Cardiac disorders

Rare	cardiomyopathy

Respiratory, thoracic and mediastinal disorders

Uncommon	dyspnoea
Rare	cough

Gastrointestinal disorders	
Very common	nausea
Common	vomiting, abdominal pain or cramps, diarrhoea
Uncommon	flatulence
Rare	pancreatitis, oral mucosa pigmentation, taste perversion, dyspepsia
Hepatobiliary disorders	
Common	elevated liver enzymes and bilirubin
Rare	severe hepatomegaly with steatosis
Skin and subcutaneous tissue disorders	
Uncommon	Rash and pruritus
Rare	nail and skin pigmentation, urticaria, sweating
Musculoskeletal and connective tissue disorders	
Common	myalgia
Uncommon	myopathy
Frequency not known	osteonecrosis
Renal and urinary disorders	
Rare	urinary frequency
Reproductive system and breast disorders	
Rare	gynaecomastia
General disorders and administration site disorders:	
Common	malaise
Uncommon	asthenia, fever. generalised pain
Rare	chest pain, influenza-like syndrome, chills
Frequency not known	immune reactivation syndrome

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

Haemoglobin concentrations in infants directly exposed to zidovudine for 6 weeks after birth 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.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

Acute overdoses of zidovudine have been reported. No specific symptoms or signs have been identified following overdosage apart from those listed as adverse events.

Treatment

Patients should be observed closely for 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 inactive glucuronide metabolite.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiretroviral for systemic use, nucleoside reverse transcriptase inhibitors, 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. It acts 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 randomised, 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 nucleoside reverse transcriptase inhibitor (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). In treatment-naïve patients infected with HIV-1, by intention-to-treat analysis, plasma HIV RNA was below 50 copies/mL in over 75% of patients after 48 weeks of combination antiretroviral treatment including zidovudine.

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).

Viral resistance

Resistance to zidovudine is developed along two patterns of multi-drug resistance mutations; the first characterised by mutations in the HIV reverse transcriptase at codons 62, 75, 77, 116 and 151 and the second involving a T69S mutation plus a 6-base pair insert at the same position, result in phenotypic resistance to AZT as well as to the other approved nucleoside reverse transcriptase inhibitors. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

Resistance to thymidine analogues (of which zidovudine is one) is well characterised and is conferred by the stepwise accumulation of up to six specific mutations in the HIV reverse transcriptase at codons 41, 67, 70, 210, 215 and 219. Viruses acquire phenotypic resistance to thymidine analogues through the combination of mutations at codons 41 and 215 or by the accumulation of at least four of the six mutations. These thymidine analogue mutations alone do not cause high-level cross-resistance to any of the other nucleosides, allowing for the subsequent use of any of the other approved reverse transcriptase inhibitors.

5.2 Pharmacokinetic properties

General	
The pharmacokinetic properties of zidovudine were evaluated in healthy adult subjects and in patients with HIV with and without liver disease	
Absorption	
Oral Bioavailability	60–70%
Food effect	No effect on extent of absorption
Distribution	
Volume of distribution (mean)	1.6 L/kg
Plasma protein binding *in vitro*	34–38%
Tissue distribution	Widely distributed, including to brain and CSF; CSF/plasma ratio 0.5
Elimination	
Mean systemic clearance (Cl/F)	1.6 L/hour/kg
Mean terminal half-life	1.1 hour [I.V], 7 hours for intracellular zidovudine triphosphate
% of dose excreted in urine	> 50–80%
% of dose excreted in faeces	NA*
Pharmacokinetic linearity	NA*
Drug interactions *(in vitro)*	
Metabolising enzymes	Uridine 5'-diphospho-glucuronosyltransferase (UGT)

NA* = Information not available

Special populations

Renal impairment

Decreased clearance result in increased exposure of zidovudine and its glucuronide metabolite. Haemodialysis and peritoneal dialysis have negligible effect on the removal of zidovudine, whereas the glucuronide metabolite elimination was enhanced.

Hepatic impairment

Limited data suggest lower clearance in patients with hepatic impairment

Elderly

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

Paediatric patients

In neonates and infants less than 14 days old, glucuronidation is reduced with a consequent increase in bioavailability, reduction in clearance and longer half-life.

In children aged over 5–6 months, the pharmacokinetic profile of zidovudine is similar to that in adults.

Pharmacokinetics in pregnancy

The pharmacokinetics of zidovudine during pregnancy were similar to that of non-pregnant women.

5.3 Preclinical safety data

General toxicity

Administration of zidovudine in animal toxicity studies at high doses was not associated with any major organ toxicity. The clinically relevant effects of zidovudine are anaemia, neutropenia and leucopenia.

Mutagenicity

Zidovudine was not mutagenic in bacterial tests but, like many nucleoside analogues, it inhibits cellular DNA replication in in vitro mammalian tests such as the mouse lymphoma assay. Zidovudine had clastogenic effects in an oral repeated-dose micronucleus test in mice.

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

Carcinogenicity

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

In oral carcinogenicity studies with zidovudine in mice and rats, late-appearing vaginal epithelial tumours were observed. The vaginal tumours were the result of long-term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study the incidence increased of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest zidovudine dose level (420 mg/kg term body weight).

In a second study, mice were given zidovudine at doses up to 40 mg/kg for 24 months; it provided no evidence that zidovudine acts as a transplacental carcinogen.

While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

Reproductive toxicology

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.

Zidovudine increased early embryonic deaths in the rabbit at relatively high systemic exposures. At maternally toxic doses, zidovudine given to rats during organogenesis increased the incidence of malformations, but there was no evidence of fetal abnormalities at lower doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Hypromellose,
magnesium stearate,
microcrystalline cellulose and
sodium starch glycolate.

Film coat (Opadry white): Hypromellose,
polyethylene glycol 400,
polysorbate 80 and
titanium dioxide.

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

NA

6.3 Shelf life

36 months: blister pack of 10 tablets (pack size: 100 tablets) and HDPE bottles of 30 and 90 tablets

48 months: HDPE bottle of 60 tablets

6.4 Special precautions for storage

Do not store above 30°C. Protect from high humidity.

6.5 Nature and contents of container

- PVDC/PVC–Aluminium blisters; 10 tablets per blister card and 10 blister cards per carton (pack size: 100 tablets).
- Round, white opaque HDPE bottle 40cc/33 MM SP 400 Neck Style M (heavy weight) sealed with induction seal and white round, polypropylene cap (pack size: 30 tablets).
- Round, white opaque HDPE bottle 50cc/33 MM SP 400 Neck Style M (heavy weight) sealed with induction seal and white round, polypropylene cap (pack size: 60 tablets)
- Round, white opaque HDPE bottle 75cc/38 MM SP 400 Neck Style M (heavy weight) sealed with induction seal and white round, polypropylene cap; (pack size: 90 tablets).

6.6 Special precautions for disposal and other handling

No special requirements.

7. SUPPLIER

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HA483

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10. DATE OF REVISION OF THE TEXT

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References

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Section 4.5

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Section 5.1

Clinical efficacy

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