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/documents/75%20SRA%20clarification_February2017_0.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA537 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 60 mg zidovudine.

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round-shaped, biconvex, film-coated tablet with plain surface on one side and scored on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA537 trade name] is indicated in antiretroviral combination therapy for human immunodeficiency virus (HIV) infected children.

[HA537 trade name] is also indicated for primary prophylaxis of HIV infection in newborn infants.

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

This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

4.2 Posology and method of administration

Oral use.
Zidovudine may be taken with or without food.
Therapy should be prescribed by a physician experienced in the management of HIV-1 infection.

Newborn infants and children weighing less than 25 kg:
Number of tablets by weight band to be taken twice daily (approximately 12 hours apart):

Number of tablets by weight band	
Weight range (kg)	**Dose**
3 to 5.9 kg	1 tablet twice daily
6 to 9.9 kg	1.5 tablets twice daily[1]
10 to 13.9 kg	2 tablets twice daily
14-19.9 kg	2.5 tablets twice daily[2]
20-24.9 kg	3 tablets twice daily

[1] This dose can either be delivered as one and a half tablets twice daily or by giving 2 tablets in the morning and 1 tablet in the evening.
[2] This dose can either be delivered as two and a half tablets twice daily or by giving 3 tablets in the morning and 2 tablets in the evening.

Dose for prevention of mother-to-child transmission (MTCT)
Start within 12 hours after birth and continue up to 6 weeks of age, depending on national recommendations.

For children weighing less than 3 kg other products with less amounts of zidovudine are

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

available. Please see the patient information leaflets of these products.

Children weighing 25 kg or more, adolescents and adults:
For these patient groups other fixed-dose formulations with higher amounts of the active substances are available.

Dosage adjustments

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 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 (creatinine clearance < 10 ml/minute), with or without haemodialysis, the dose should be reduced by 30-50%.

4.3 Contraindications

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

Zidovudine is contraindicated in patients with abnormally low neutrophil counts ($< 0.75 \times 10^6$/l) or low haemoglobin (< 7.5 g/dl or 4.7 mmol/l).

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

4.4 Special warnings and precautions for use

Transmission of HIV

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Other drugs

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

Haematological Adverse Reactions

Anaemia, neutropenia and leukopenia (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 $< 1.0 \times 10^9$/L) occurs during treatment with zidovudine.

Liver disease

Caution should be exercised when administering nucleoside reverse transcriptase inhibitors (NRTIs), including zidovudine, to any patient with liver disease.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients with chronic hepatitis B or C treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please also refer to the relevant product information for these medicinal products. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

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 older patients, 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 nucleoside reverse transcriptase inhibitor (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 lactate 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 disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to 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.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampicin

Limited data suggest that co-administration of zidovudine with rifampicin decreases the AUC (area under the plasma concentration curve) of zidovudine by 48% ± 34%. This may result in a partial loss or total loss of efficacy of zidovudine. The concomitant use of rifampicin with zidovudine should be avoided (see section 4.4).

Stavudine

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

Probenecid

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

Lamivudine

A modest increase in C_{max} (28%) was observed for zidovudine when administered with lamivudine, but overall exposure (AUC) was not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Phenytoin

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

Atovaquone

Zidovudine does not appear to affect the pharmacokinetics of atovaquone. However, pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a three-week, concomitant course of atovaquone for the treatment of acute PCP would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.

Valproic acid, fluconazole and methadone

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

Ribavirin

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination antiretroviral regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

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.

Other information

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

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

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

A large amount of data on pregnant women indicate that zidovudine does not cause congenital malformations or cause significant foetal or neonatal toxicity.

Studies in pregnant rats and rabbits given zidovudine orally at dosage levels up to 450 and 500 mg/kg/day respectively during the major period of organogenesis have revealed no evidence of teratogenicity. There was, however, a statistically significant increase in fetal resorptions in rats given 150 to 450 mg/kg/day and in rabbits given 500 mg/kg/day.

Zidovudine can be used during pregnancy if clinically needed, but a risk to the foetus 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 [HA537 trade name] 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 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).

Also, zidovudine has been associated with 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 organ system and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), very rare (<1/10 000), or not known (cannot be estimated from the available data).

Organ system	Very common or common	Uncommon or rare	Very rare	Not known
Blood and lymphatic	Anaemia, leukopenia, neutropenia	Thrombocytopenia, pancytopenia, red cell aplasia	Aplastic anaemia	
Metabolic and nutrition		Lactic acidosis		Lipodystrophy, insulin resistance, hyperglycemia, hyperlipidaemia, hyperlactataemia
Psychiatric		Anxiety, depression		
Nervous system	Headache, dizziness	Insomnia, loss of mental acuity. somnolence,		

Organ system	Very common or common	Uncommon or rare	Very rare	Not known
		paraesthesia, convulsions		
Cardiac		Cardiomyopathy		
Respiratory		Dyspnoea, cough		
Gastrointestinal	Nausea. Vomiting, diarrhoea, abdominal pain	Flatulence, pancreatitis, oral mucosal pigmentation, dysgeusia, dyspepsia		
Hepatobiliary	Transient elevation of liver enzymes and bilirubin	Severe hepatomegaly with steatosis		
Reproductive and breast		Gynaecomastia		
Skin and subcutaneous tissue		Rash, pruritis, nail and skin pigmentation, urticaria, sweating		
Musculoskeletal and connective tissue	Myalgia	Myopathy		Osteonecrosis
General disorders	Malaise	Asthenia, fever, generalised pain, chest pain, influenza-like syndrome, chills		Immune reconstitution syndrome
Renal and urinary		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 postpartum 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

Acute overdoses of zidovudine have been reported. These involved exposures up to 50 g. 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 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. 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 nucleoside reverse transcriptase inhibitor (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (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.

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

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 analogue 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.

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 0.6
Elimination	
Mean systemic clearance (Cl/F)	1.6 L/hr/kg
Mean terminal half-life	1.1 hr
% of dose excreted in urine	14% unchanged, 74% as glucuronide
% of dose excreted in faeces	NA
Pharmacokinetic linearity	Linear.
Drug interactions *(in vitro)*	
Metabolising enzymes	Glucuronidation to form inactive glucuronide
Special populations	
Renal impairment	Decreased clearance resulting in increased exposure of zidovudine and its glucuronide metabolite. Hemodialysis and peritoneal dialysis appeared to have a 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 patients	NA
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

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

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

Film coat: hypromellose, polyethylene glycol 400, polysorbate 80 and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Blisters: Do not store above 30ºC. Protect from high humidity. Store tablets in blisters in the provided carton.

Bottles: Do not store above 30ºC. Protect from high humidity

6.5 Nature and contents of container

Clear PVC/PVDC–Aluminium blisters; 10 tablets per blister card and 10 blister cards per carton (pack size: 100 tablets).

Round, opaque white HDPE bottle with polypropylene child resistant cap (Pack sizes: 60, 100, 500 and 1000).

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed off in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA537

9. DATE OF PREQUALIFICATION

14 June 2013

10. DATE OF REVISION OF THE TEXT

October 2020

References

This text is primarily based on the European SmPC for Zidovudine, available at: http://www.medicines.org.uk/EMC/medicine/10419/SPC/Zidovudine+100+mg+10+ml%2c+oral+solutio n/

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/