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

[HA572 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 30 mg lamivudine and 60 mg zidovudine.

Excipients with potential clinical effect

Each dispersible tablet contains 18 mg aspartame.

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Dispersible tablet

White to off-white, round, uncoated dispersible tablets. They are biconvex tablet (rounded on top and bottom) with a bevelled edge. The tablets have a break line on one side with “LZ” debossed (stamped into the tablet) to the left and “1” debossed (stamped into the tablet) to the right of the break line. they are debossed (stamped into the tablet) with "M" on the other side.

The break line is intended for subdivision of [HA572 trade name] tablets into equal doses when half a tablet dose is to be administered.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA572 trade name] is indicated as part of antiretroviral combination therapy for the treatment of HIV-1 infection in infants and children aged from 4 weeks and weighing from 3 kg to 25 kg.

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

For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g. those of the WHO should be consulted.

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.

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

Posology

Infants and children aged over 4 weeks

Child's weight	**Dose**	
	[HA572 trade name] tablets	**active substance in mg**
3 to less than 6 kg	1 tablet each morning and evening	Lamivudine 30 mg + zidovudine 60 mg each morning and evening
6 to less than 10 kg	1½ tablets each morning and evening	Lamivudine 45 mg + zidovudine 90 mg each morning and evening
10 to less than 14 kg	2 tablets each morning and evening	Lamivudine 60 mg + zidovudine 120 mg each morning and evening
14 to less than 20 kg	2½ tablets each morning and evening	Lamivudine 75 mg + zidovudine 150 mg each morning and evening
20 to less than 25 kg	3 tablets each morning and evening	Lamivudine 90 mg + zidovudine 180 mg each morning and evening

Patients weighing above 25 kg

[HA572 trade name] is not intended for patients weighing more than 25 kg. Formulations containing higher amounts of lamivudine and zidovudine are more suitable.

Elderly

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

Renal impairment

Since dose adjustment may be necessary in patients with severe renal impairment (creatinine clearance less than 30 mL/minute), it is recommended that separate preparations of lamivudine and zidovudine are used.

Hepatic impairment

Data from patients with moderate to severe hepatic impairment show that hepatic dysfunction does not affect lamivudine pharmacokinetics significantly. However, limited data in patients with cirrhosis suggest that zidovudine may accumulate in patients with hepatic impairment because of decreased glucuronidation. As zidovudine doses may need to be adjusted, it is recommended that separate preparations or other formulations of lamivudine and zidovudine are used in patients with severe hepatic impairment.

Haematological adverse reactions

Since substitution or dose reduction of zidovudine should be considered in patients whose haemoglobin concentrations or neutrophil counts fall in a clinically significant way, it is recommended that separate preparations of lamivudine and (if appropriate) zidovudine be administered (see section 4.4).

Missed dose

If a dose is missed and this is noticed within 6 hours, the patient should take the missed dose as soon as possible. The patient should then take the next regular dose at the usual time. If it is longer since the missed dose, the patient should take the normal dose when it is next due. No double dose should be given to make up for a forgotten dose.

Method of administration

Oral use

[HA572 trade name] can be taken with food or between meals.

The tablets should be dispersed in drinking water. Each tablet should be dispersed in about 10 mL water.

Please refer to section 6-6 for further instructions.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
[HA572 trade name] must **not** be used in patients with:

- abnormally low neutrophil count (less than 0.75×10^9/L) (see section 4.4),
- abnormally low haemoglobin (less than 75 g/L or 4.65 mmol/L) (see section 4.4).

4.4 Special warnings and precautions for use

Dose adjustment

It is recommended that separate preparations or other formulations of lamivudine and zidovudine are used for any dosage adjustment (see section 4.2).

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 [HA572 trade name], e.g. as follows:

- 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.

Since substitution, dose reduction or interruption of zidovudine therapy may be necessary in patients whose haemoglobin concentration or neutrophil count fall in a clinically significant way, separate preparations or other formulations of lamivudine and (if appropriate) zidovudine should be used.

Pancreatitis

Treatment with [HA572 trade name] should be stopped immediately if signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

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 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.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues can cause mitochondrial damage. Mitochondrial dysfunction has been reported in HIV-negative infants exposed to nucleoside analogues in utero 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 utero to nucleoside and nucleotide analogues who has severe features of unknown aetiology, particularly neurological effects.

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-containing products. 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.

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.

Liver disease

[HA572 trade name] should be used with caution in any patient with chronic hepatitis B infection. Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication and discontinuation of lamivudine or virological failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. If [HA572 trade name] is discontinued in a patient with HBV infection, the patient should be periodically monitored, both clinically and by assessment of liver function tests (ALT and bilirubin levels) and markers of HBV replication, for at least 4 months, and then as clinically indicated.

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.

Patients with liver dysfunction have an increased risk of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If liver disease worsens in such patients, interruption or discontinuation of therapy should be considered.

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease or long-term exposure to combination antiretroviral therapy. Additional risk factors for this condition include corticosteroid use, alcohol consumption, severe immunosuppression and higher body mass index. Patients should be advised to seek medical advice if they develop joint aches and pain, joint stiffness or difficulty in movement.

Renal Impairment

Patients with creatinine clearance between 30 and 49 mL/minute receiving [HA572 trade name] may have 1.6- to 3.3-fold higher lamivudine exposure (AUC) than patients with creatinine clearance more than 50 mL/minute. Patients with creatinine clearance between 30 and 49 mL/minute should be monitored for lamivudine-related adverse events, notably haematologic toxicity. If neutropenia or anaemia worsen, lamivudine dose should be reduced.

Excipients

[HA572 trade name] contains 18 mg aspartame in each tablet. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Lamivudine undergoes limited metabolism and is almost completely eliminated via the kidneys. Active renal secretion of lamivudine is mediated by organic cation transporters (OCT). Co-administration of lamivudine with OCT inhibitors or nephrotoxic drugs may increase lamivudine exposure.

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.

Lamivudine and zidovudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and do 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.

[HA572 trade name] interactions

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
HIV antiretrovirals		
Emtricitabine with lamivudine	Potential competition for metabolism.	Emtricitabine should not be co-administered with [HA572 trade name].
Stavudine with zidovudine	In vitro antagonism of anti-HIV activity between stavudine and zidovudine could result in decreased efficacy of both drugs.	Stavudine should not be co-administered with [HA572 trade name].
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-administered 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 [HA572 trade name] and clarithromycin should be separated by at least 2 hours.
Dapsone with zidovudine	Potential renal and haematological toxicity	Renal function and haematological parameters should be monitored and dose reduction should be considered.
Trimethoprim + sulfamethoxazole with lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑ 40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (Organic cation transporter inhibition)	No dosage adjustment of [HA572 trade name] is necessary, unless patient has renal impairment. When concomitant administration with trimethoprim + sulfamethoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim + sulfamethoxazole for treating *Pneumocystis jirovecii* pneumonia and toxoplasmosis have not been studied and should be avoided.

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Trimethoprim + sulfamethoxazole with zidovudine	Potential renal and haematological toxicity	Renal function and haematological parameters should be monitored and dose reduction should be considered.
Sulfadiazine with lamivudine	Sulfadiazine is associated with renal toxicity and in some cases renal failure. Potential for renal toxicity as lamivudine is mainly excreted by active renal transport.	Renal function should be monitored.
Sulfadiazine with zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Vancomycine and zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Antifungal		
Amphotericin B and zidovudine	Potential renal and haematological toxicity	Renal function and haematological parameters should be monitored and dose reduction should be considered.
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 monitor for signs of zidovudine toxicity (section 4.8).
Flucytosine with lamivudine	Potential for haematological toxicity	Haematological parameters should be monitored, and dose reduction should be considered
Flucytosine with zidovudine	Potential renal and haematological toxicity	Renal function and haematological parameters should be monitored and dose reduction should be considered
Antimalarial		
Amodiaquine and zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Primaquine and zidovudine	Potential haematological toxicity	Haematological parameters should be monitored
Antimycobactrial		
Rifampicin and zidovudine (600 mg daily/200 mg three times daily)	Zidovudine AUC ↓48%	Insufficient data to recommend dosage adjustment
Antipsychotics		
Fluphenazine with zidovudine Quetiapine with zidovudine	Potential haematological toxicity.	Haematological parameters should be monitored
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.

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
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.
Cladribine with lamivudine	Interaction not studied In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential loss of cladribine efficacy. Some clinical findings also support a possible interaction between lamivudine and cladribine	Concomitant use of lamivudine with cladribine is not recommended.
Cisplatin with lamivudine	Potential renal toxicity	Renal function should be monitore
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
Doxorubicin with zidovudine	Potential renal and haematological toxicity.	Concomitant use of doxorubicin and zidovudine is not advised. However, if used, renal function and haematological parameters should be monitored, and dose reduction considered.
Vinblastine with zidovudine Vincristine with zidovudine	Potential renal and haematological toxicity	Renal function and haematological parameters should be monitored and dose reduction should be considered.

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 zidovudine toxicity.
Miscellaneous		
Methyldopa with zidovudine	Potential haematological toxicity.	Haematological parameters should be monitored
Sorbitol solution (3.2 g, 10.2 g, 13.4 g) with lamivudine, single dose lamivudine oral solution 300 mg	Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%: 55%	When possible, chronic co-administration of [HA572 trade name] should be avoided with medicines containing sorbitol or other osmotic-acting poly-alcohols (e.g. xylitol, mannitol, lactitol, maltitol). More frequent monitoring of HIV-1 viral load should be considered when chronic co-administration cannot be avoided

↓	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)

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, pyrimethamine, ganciclovir, and interferon) and zidovudine may increase the risk of adverse reactions. If concomitant therapy with [HA572 trade name] and any of these medicines is necessary then extra care should be taken to monitor renal function and haematological parameters and, if required, the dose 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 lamivudine or for zidovudine (www.apregistry.com). A large amount of cumulative information on pregnant women taking lamivudine or 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. No such data are available for lamivudine.

Consideration should be given to possibility of recurrence of hepatitis on discontinuation of lamivudine in patients who are co-infected with hepatitis and were treated with lamivudine containing medicines such as [HA572 trade name] and who subsequently become pregnant.

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 utero or postnatally to nucleoside analogues.

Breast-feeding

Both lamivudine and zidovudine are 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

Neither zidovudine nor lamivudine have impaired fertility in studies in male and female rats. There are no data on their effect 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

[HA572 trade 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

[HA572 trade name] contains lamivudine and zidovudine and adverse reactions associated with each of the active substances may be expected. There is no evidence of added toxicity with concurrent administration of the two active substances.

The most frequently reported adverse reactions are headache and nausea. The most common serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia (see section 4.4).

The undesirable effects of [HA572 trade 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, insomnia
Rare	paraesthesia, somnolence, loss of mental acuity, convulsions

Cardiac disorders

Rare	cardiomyopathy

Respiratory, thoracic and mediastinal disorders

Common	cough, nasal symptoms
Uncommon	dyspnoea

Gastrointestinal disorders

Very common	nausea
Common	vomiting, abdominal pain or cramps, diarrhoea
Uncommon	flatulence
Rare	pancreatitis, raised serum amylase, oral mucosa pigmentation, taste perversion, dyspepsia

Hepatobiliary disorders

Common	elevated liver enzymes and bilirubin
Rare	hepatitis, severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders

Common	rash, hair loss
Uncommon	pruritus
Rare	nail and skin pigmentation, urticaria, sweating, angioedema

Musculoskeletal and connective tissue disorders

Common	arthralgia, myalgia
Uncommon	myopathy
Rare	rhabdomyolysis
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, fatigue, fever
Uncommon	asthenia, generalised pain
Rare	chest pain, influenza-like syndrome, chills
Frequency not known	immune reactivation syndrome

See also sections 4.4 and 4.5.

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.

For reporting of adverse events and PV related queries please write to Email: ProductSafety@viatris.com

4.9 Overdose

There is limited experience of overdosage with lamivudine and zidovudine. No specific signs and symptoms have been identified following acute overdose with lamivudine or zidovudine apart from those listed as undesirable effects. No fatalities occurred and the patients recovered.

If overdose occurs, patients should be monitored for toxicity (see section 4.8), and standard supportive treatment given as necessary. Since elimination of lamivudine and the glucuronide metabolite of zidovudine are enhanced by haemodialysis, continuous haemodialysis could be used in the treatment of overdosage but this has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC Code J05AR01

Mechanism of action

Lamivudine and zidovudine are nucleoside analogues that are active against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both compounds are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-triphosphate, respectively. Their main modes of action are as chain terminators of viral reverse transcription.

Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication in vitro; lamivudine is also active against zidovudine-resistant clinical isolates of HIV.

Clinical efficacy

In clinical trials, lamivudine and zidovudine in combination with a third antiretroviral agent reduce HIV-1 viral load and increases CD4 cell count. In a trial of zidovudine and lamivudine in combination with efavirenz, plasma HIV RNA was < 50 copies/mL in 68% of patients after 48 weeks, by intention-to-treat analysis. Lamivudine and zidovudine have been widely used as components of antiretroviral combination therapy with other antiretroviral agents.

Resistance

In the great majority of cases when combination antiretroviral therapy comprising zidovudine and lamivudine fails virologically, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine. In vitro data suggest that continuation of lamivudine in antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). However, clinical data are very limited and preclude any reliable conclusion. Therefore, continuing lamivudine therapy despite emergence of M184V mutation should be considered only when other effective nucleoside reverse transcriptase inhibitors (NRTIs) are not available.

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.

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 zidovudine as well as to the other approved NRTIs. Either of these two patterns of multinucleoside resistance mutations severely limits future therapeutic options.

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

The combination of lamivudine and zidovudine has not been specifically investigated in HIV patients co-infected with HBV.

5.2 Pharmacokinetic properties

The absorption characteristics were determined following single dose administration of 2 x [HA572 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± Standard deviation (geometric mean)**	
	Lamivudine	**Zidovudine**
Maximum concentration (C_{max})	667 ng/ml (±199)	866 ng/ml (± 288)
Area under the curve (AUC_{0-inf}), a measure of the extent of absorption	3105 ng h/ml (±691)	1131 ng h/ml (±269)
Time to attain maximum concentration (T_{max})	0.83 (0.50-2.5) hour	0.33 (0.17-0.83) hour

Pharmacokinetics of Lamivudine and Zidovudine

	Lamivudine	**Zidovudine**
Absorption		
Oral bioavailability	80–85%	60–70%
Distribution		
Volume of distribution (mean)	1.3 L/kg	1.6 L/kg
Plasma protein binding in vitro	< 36%	34–38%
Tissue distribution	CSF/plasma ratio 0.12	CSF/plasma ratio 0.5
Metabolism		
	Only minor route (5–10%)	Glucuronidation Major metabolite: 5'-zidovudine-glucuronide
Active metabolite(s)	None	None
Elimination		
Elimination half life	18–19 hours 16–19 hours for intracellular lamivudine triphosphate	1.1 hours [IV] 7 hours for intracellular zidovudine triphosphate
Mean systemic clearance (Cl/F)	0.32 L/hour/kg	1.6 L/hour/kg
% of dose excreted in urine	> 70% (predominantly cleared unchanged)	> 50–80%
% of dose excreted in faeces	NA*	NA*
Pharmacokinetic linearity	Linear pharmacokinetics	NA*
Drug interactions (in vitro)		
Transporters	OCT (organic cationic transporters)	
Metabolising enzymes	–	UGT- Uridine 5'-diphospho-glucuronosyltransferase

NA* = Information not available

Pharmacokinetics in pregnancy

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

Pharmacokinetics in children

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

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults

5.3 Preclinical safety data

General toxicity

The clinically relevant effects of lamivudine and zidovudine in combination are anaemia, neutropenia and leucopenia.

Mutagenicity and carcinogenicity

Lamivudine and zidovudine were not mutagenic in bacterial tests but, like many nucleoside analogues, they inhibit cellular DNA replication in in vitro mammalian tests such as the mouse lymphoma assay. Lamivudine has not shown any genotoxic activity in in vivo studies at doses that produced plasma concentrations up to 40–50 times higher than clinical plasma levels. Zidovudine showed 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.

The carcinogenic potential of a combination of lamivudine and zidovudine has not been tested. In oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. 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 zidovudine an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight) were seen.

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months. The second study thus 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

Lamivudine has demonstrated evidence of increased early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in humans, but not in the rat even at very high systemic exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of fetal abnormalities was observed at lower doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

colloidal silicon dioxide

sodium starch glycolate

croscarmellose sodium

aspartame

magnesium stearate

strawberry flavour (containing natural flavours and maltodextrin)

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

HDPE bottle

Round wide mouth opaque white HDPE bottle with white opaque polypropylene screw cap, containing absorbent cotton.

Pack size: 60 tablets.

6.6 Special precautions for disposal and other handling

Preparation and administration - extemporaneous formulation for children

Instructions for use

1. Pour into a small clean cup a small amount of drinking water (about 10 mL or 2 teaspoonfuls for each tablet)
2. Add the right number of tablets to the water and swirl it until each tablet has broken down completely
3. Get your child to drink all the mixture at once
4. Add another 10 mL (2 teaspoonfuls) to the cup, swirl it again and ask your child to drink this also. This makes sure that the child receives the full dose.

Do not disperse [HA572 trade name] in any liquid other than drinking water.

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA572

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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Section 5.1

Clinical efficacy

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