

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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA668 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 300 mg of lamivudine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The tablets are grey coloured, modified diamond shaped, biconvex, bevelled edge film coated tablets, debossed with 'A' on one side and '101' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA668 trade name] is indicated as part of antiretroviral combination therapy for the treatment of HIV-1 infection in adults, adolescents and children weighing at least 25 kg.

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

[HA668 trade name] may be used as part of a regimen for post-exposure prophylaxis to HIV. For use of antiretroviral agents for post-exposure prophylaxis the most recent official guidelines, e.g. those by 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.

Adults, adolescents and children (weighing at least 25 kg):

The recommended dose of lamivudine is 300 mg daily.

Children weighing less than 25 kg

[HA668 trade name] is not suitable for children weighing less than 25 kg. For these patients another formulation should be used, e.g. a tablet that can be given at a smaller dose or an oral solution of lamivudine.

Special populations

Older people

No specific data are available; however, special care is advised due to age-associated changes such as the decrease in renal function and alteration of haematological parameters.

Liver Impairment

No dose adjustment is necessary.

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

Renal Impairment

Lamivudine concentrations are increased in patients with moderate or severe renal impairment due to decreased clearance. It is recommended that lamivudine dose be modified in patients with reduced creatinine clearance as shown below.

It may be necessary to use alternative formulations such as lamivudine oral solution for patients whose creatinine clearance falls below 30 mL/minute (see below).

Dosing for patients weighing up to 25 kg with renal impairment

Creatinine clearance	First dose	Subsequent doses
At least 50 mL/minute	300 mg or 150 mg	300 mg once daily or 150 mg twice daily
30–50 mL/minute	150 mg	150 mg once daily
15–30 mL/minute*	150 mg	100 mg once daily
5–15 mL/minute*	150 mg	50 mg once daily
Less than 5 mL/minute*	50 mg	25 mg once daily
* An alternative formulation such as an oral solution is required for patients with creatinine clearance of less than 30 mL/minute		

[HA668 trade name] cannot be halved. Please use alternative formulation when smaller doses are required.

Method of administration

[HA668 trade name] may be taken with food or between meals. Preferably, the tablet should be swallowed whole.

For patients with difficulty swallowing tablets, other lamivudine formulations, e.g., oral solution, may be available. If these are not available, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

[HA668 trade name] is not recommended for use as monotherapy.

Renal impairment

In patients with moderate to severe renal impairment, the terminal plasma half-life of lamivudine is increased due to decreased clearance, therefore the dose should be adjusted (see section 4.2).

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when lamivudine was combined with tenofovir disoproxil and abacavir as well as with tenofovir disoproxil and didanosine as a once-daily regimen.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may cause a variable degree of mitochondrial damage. This is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed to nucleoside analogues either in utero or after birth; these have predominantly involved regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasemia). These events have often been transitory. Late-onset neurological disorders have been

reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown.

Mitochondrial damage should be considered for any child exposed in utero to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown aetiology, particularly neurologic findings. These findings do not affect current guidelines on the use of antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Weight and metabolic parameters

Weight and levels of blood lipids and glucose may increase 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 there is no strong evidence relating weight gain to any particular treatment. Established HIV treatment guidelines should be consulted for advice on monitoring of blood lipids and glucose. Lipid disorders should be managed as clinically appropriate.

Pancreatitis

Cases of pancreatitis have occurred rarely. However, it is not clear whether these cases were due to the antiretroviral treatment or to the underlying HIV disease. Treatment with [HA668 trade name] should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

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.

Opportunistic infections

Patients receiving [HA668 trade name] or other antiretroviral medicines may still develop opportunistic infections and other complications of HIV infection. Therefore, health care providers experienced in the treatment of these associated HIV diseases should keep patients under close clinical observation.

Liver disease

Lamivudine should be given cautiously to patients with hepatitis B coinfection. Lamivudine inhibits hepatitis B virus (HBV) replication. Discontinuation of lamivudine or virologic failure resulting from HBV developing resistance to lamivudine may cause hepatic deterioration and a hepatitis flare. Periodic monitoring of liver function and markers of HBV replication is recommended for at least 4 months if lamivudine is discontinued in HBV-coinfected patients.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at higher risk of severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, refer also to the product information for these medicines.

If [HA668 trade name] is discontinued in patients coinfecting with hepatitis B virus, periodic monitoring of liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Patients with liver dysfunction, including chronic active hepatitis, have higher frequency 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 treatment must be considered (see section 4.8).

Paediatric population

A study (see section 5.1) found lower rates of virologic suppression and more frequent viral resistance in children receiving lamivudine oral solution compared to those receiving tablets. Lamivudine should preferably be used as tablet formulation in children.

Osteonecrosis

Osteonecrosis has been reported, particularly in patients with advanced HIV-disease or after long-term combination antiretroviral therapy. Its aetiology is considered to be multifactorial and includes corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index. Patients should be advised to seek medical advice if they have joint aches and pain, joint stiffness or movement difficulty.

Drug Interactions

[HA668 trade name] should not be taken with any other medicine that contains lamivudine.

Because of overlapping resistance and lack of additive antiretroviral effects, [HA668 trade name] should not be taken with emtricitabine (see section 4.5).

The combination of lamivudine with cladribine is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Metabolic interactions with lamivudine are less likely because of its limited metabolism and plasma protein binding and almost complete renal clearance.

Lamivudine metabolism does not involve CYP3A and interactions with medicines metabolised by this system (e.g. protease inhibitors) are unlikely.

Sulfamethoxazole/trimethoprim increases plasma concentrations of lamivudine but a clinically significant effect is not expected; the patient should be monitored for lamivudine toxicity in case of marked renal impairment or if high doses of sulfamethoxazole/trimethoprim are used (e.g. for treating *Pneumocystis jirovecii* pneumonitis).

Medicines which are mainly eliminated by renal secretion via the organic cationic transport system, e.g. trimethoprim, may interact with lamivudine. Medicines (e.g. ranitidine, cimetidine), which are eliminated only in part by this mechanism, were shown not to interact with lamivudine.

Due to similarities, [HA668 trade name] should not be administered concomitantly with other cytidine analogues, such as emtricitabine.

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine, raising the possibility of a loss of cladribine's efficacy if the two are used concomitantly. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended.

Co-administration of sorbitol solution (3.2, 10.2, and 13.4 g) with a single 300-mg dose of lamivudine oral solution to adults resulted in dose-dependent decreases of 14, 32, and 36% in lamivudine exposure (AUC_{∞}) and 28, 52, and 55% in the C_{max} of lamivudine. When possible, chronic co-administration of lamivudine with medicines containing sorbitol or other osmotic-acting polyalcohols or monosaccharide alcohols (e.g. lactitol, maltitol, mannitol, xylitol) should be avoided. More frequent monitoring of HIV-1 viral load should be considered when chronic co-administration cannot be avoided.

The co-administration of sulfadiazine and cisplatin with lamivudine has a potential for renal toxicity and would require monitoring of renal function.

The co-administration of flucytosine with lamivudine has potential for haematological toxicity which requires monitoring of haematological parameters and dose reduction should be considered.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

WHO HIV Treatment guidelines recommend lamivudine-containing therapy for pregnant women and women of childbearing potential.

No increased risk of birth defects has been reported for lamivudine (www.apregistry.com).

Breastfeeding

Lamivudine 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

Studies in animals showed that lamivudine had no effect on fertility (see section 5.3).

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.

Nevertheless, the clinical status of the patient and the adverse reaction profile of [HA668 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

The following adverse reactions have been reported during therapy for HIV disease with lamivudine.

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

System Organ Class	Common	Uncommon	Rare	Very Rare
Blood and lymphatic system disorders		Neutropenia and anaemia (both occasionally severe), thrombocytopenia		Pure red cell aplasia
Metabolism and nutrition disorders				Lactic acidosis
Nervous system disorders	Headache, insomnia			Peripheral neuropathy (or paraesthesia)
Respiratory, thoracic and mediastinal disorders	Cough, Nasal symptoms			
Gastrointestinal disorders	Nausea, vomiting, abdominal pain or cramps, diarrhoea		Pancreatitis, elevations in serum amylase	
Hepatobiliary disorders		Transient elevations in liver	Hepatitis	

		enzymes (AST, ALT)		
Skin and subcutaneous tissue disorders	Rash, alopecia		Angiooedema	
Musculoskeletal and connective tissue disorders	Arthralgia, muscle disorders		Rhabdomyolysis	
General disorders and administration site conditions	Fatigue, malaise, fever			

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

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 these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral exposure. The frequency of which is unknown (see section 4.4).

Paediatric population

1206 HIV-infected paediatric patients aged 3 months to 17 years were enrolled in a clinical trial, 669 of whom received abacavir and lamivudine either once or twice daily (see section 5.1). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

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

No specific symptoms or signs have been identified following acute overdose with lamivudine, apart from those listed as undesirable effects.

If overdose occurs the patient should be monitored for toxicity (see section 4.8), and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis may be used to treat an overdose, but this has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside and nucleotide reverse transcriptase inhibitor, ATC Code: J05AF05.

Mechanism of action

Lamivudine is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'-triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication in vitro, it is also active against zidovudine-resistant

clinical isolates of HIV. No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine).

Resistance

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTI's should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTI's are available.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*.

Clinical efficacy and safety

Lamivudine has been investigated in several randomised, prospective clinical trials in combination with other antiretroviral drugs. These studies demonstrate significant decrease in plasma HIV RNA and increase in CD4 cell counts when lamivudine is used in combination with another nucleos(t)ide analogue and third agent of a different therapeutic class, e.g. a non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) or integrase strand transfer inhibitor (INSTI). In recent studies by intention-to-treat analysis 88% of subjects achieved plasma HIV RNA \leq 50 copies/ml after 48 weeks of combination antiretroviral treatment.

Paediatric subjects

Clinical trial evidence from paediatric patients receiving lamivudine with other antiretroviral drugs (abacavir, nevirapine/efavirenz or zidovudine) has shown that the resistance profile observed in paediatric patients is similar to that observed in adults, in terms of the genotypic substitutions detected and their relative frequency.

In a randomised clinical trial, the safety and efficacy of once-daily dosing with twice-daily dosing of lamivudine and abacavir, in combination with a third antiretroviral drug was compared in 1206 paediatric patients aged 3 months to 17 years. After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/ml at Week 48 as well as at Week 96. Analyses by formulation demonstrated the proportion of subjects with HIV-1 RNA of less than 80 copies per mL at randomisation and Week 96 was higher in subjects who had received tablet formulations of lamivudine and abacavir (75% [458/610] and 72% [434/601]) than in those who had received any solution formulation(s)-at any time (with lamivudine solution given at weight band-based doses approximating 8 mg per kg per day)

(52% [29/56] and 54% [30/56]), respectively. These differences were observed in each different age group evaluated. See section 4.4.

5.2 Pharmacokinetic properties

The absorption characteristics of [HA668 trade name] have been determined after administration of tablets of [HA668 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value \pm standard deviation arithmetic mean \pm SD
Maximum concentration (C_{max}) ng/ml	3225 \pm 798
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.hour/ml	14430 \pm 2472
Time to attain maximum concentration (t_{max}) hour	1.28 \pm 0.74

Pharmacokinetics of lamivudine

Absorption	
Oral bioavailability	80–85%
Food effect	not clinically relevant
Distribution	
Volume of distribution (mean)	1.3 L/kg
Plasma protein binding in vitro	< 36%
Metabolism	
	Only minor route (< 10%)
Active metabolite(s)	Information not available
Elimination	
Elimination half life	18-19 h 16-19 h for intracellular lamivudine triphosphate
Mean systemic clearance	0.32 L/h/kg
% of dose excreted in urine	> 70% [predominantly cleared unchanged]
Pharmacokinetic linearity	Linear pharmacokinetics
Drug interactions (<i>in vitro</i>)	
Transporters	OCT (organic cationic transporters)

Pharmacokinetics in pregnancy

The pharmacokinetics of lamivudine and zidovudine during pregnancy were similar to that of non-pregnant women. Nevirapine clearance increases in pregnant women resulting in lower AUC and C_{max} compared to non-pregnant women.

Pharmacokinetics in children

The absolute bioavailability of lamivudine (about 58–66%) was reduced in children below 12 years of age. Paediatric pharmacokinetic studies with both oral solution and tablet formulations found that once-daily dosing provides equivalent AUC_{0-24h} to twice-daily dosing of the same total daily dose.

5.3 Preclinical safety data

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia.

Mutagenicity and carcinogenicity

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an in vitro cytogenetic assay and the mouse lymphoma assay. Based on the totality of the available data it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment. The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential relevant for humans.

Reproductive toxicology

In reproductive toxicity studies in animals, lamivudine was shown to cross the placenta. Lamivudine was not teratogenic in animal studies and data on early embryonic deaths were not consistent between species. Data from monkey studies demonstrated that foetuses exposed in utero to the combination of zidovudine and lamivudine sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

A fertility study in rats has shown that lamivudine had no effect on male or female fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Microcrystalline cellulose
Sodium starch glycolate
Povidone
Magnesium stearate

Film coat: Hypromellose
Titanium dioxide
Macrogol/PEG
Polysorbate
Iron oxide black

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

36 months

6.4 Special precautions for storage

Store below 30°C. Store in the original container.

6.5 Nature and contents of container

White opaque HDPE bottle with white polypropylene child resistant cap and an induction sealer.

Each bottle contains 30 tablets.

6.6 Special precautions for disposal and other handling

Not applicable

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA668

9. DATE OF PREQUALIFICATION

21 January 2019

10. DATE OF REVISION OF THE TEXT

May 2023

References

General reference sources for this SmPC include:

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition. Geneva: World Health Organization; 2016

(<https://apps.who.int/iris/handle/10665/208825>)

Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations: 2022(7) <https://www.who.int/publications/i/item/9789240052390>

Consolidated guidelines on hiv prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach.2021., available at: <https://www.who.int/publications/i/item/9789240031593>

European SmPCs of Epivir available at:

https://www.ema.europa.eu/en/documents/product-information/epivir-epar-product-information_en.pdf

Further references relevant to sections of the SmPC include:

Section 4.4

On combination therapy

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Section 4.6

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On resistance

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The Stanford HIV drug resistance database. Available at: <http://hivdb.stanford.edu/>
Castagna *et al.* *AIDS* **2006**;20:795-803

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