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 (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

1. NAME OF THE MEDICINAL PRODUCT

[HA644 trade name]*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg lamivudine.

For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Film coated tablet

White, round shaped, biconvex, film coated tablet with bevelled edge, scored on one side and debossed with 'I08' on the other side.

The score-line is only to facilitate breaking for ease of swallowing and not to divide into equal dose.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA644 trade name] is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults, adolescents and children weighing at least 25 kg.

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

For use of antiretroviral agents for post-exposure prophylaxis consult the most recent official guidelines (e.g. those of the WHO).

4.2 Posology and method of administration

The therapy should be initiated 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 [HA644 trade name] is 300 mg daily. This may be administered as either one 150 mg twice daily or 300 mg (2 x 150 mg tablets) once daily (see section 4.4).

Children weighing less than 25 kg
This product should not be used in children weighing less than 25 kg since appropriate dose adjustments cannot be made. For these patients another formulation should be used, e.g. a tablet which can be used to give a smaller dose of lamivudine or an oral solution.

To ensure administration of the entire dose, the tablet should be swallowed whole.
For patients who are not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

[HA644 trade name] may be taken with food or between meals.

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

Hepatic Impairment
Data obtained in patients with moderate to severe hepatic impairment shows that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose

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

adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

Renal Impairment
Lamivudine concentrations are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted, using oral solution presentation of lamivudine for patients whose creatinine clearance falls below 30 ml/min (see tables).

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

Creatinine clearance (ml/min)	First dose	Maintenance dose
≥ 50	300 mg or 150 mg	300 mg once daily 150 mg twice daily
30 - 49	150 mg	150 mg once daily
15 - 29*	150 mg	100 mg once daily
5 - 14*	150 mg	50 mg once daily
< 5*	50 mg	25 mg once daily
*Another formulation such as an oral solution is required for patients with creatinine clearance of less than 30 ml/minute		

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
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.

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 impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, 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. These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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 life style. For lipids, there is in some cases evidence for

a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. 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 [HA644 trade name] should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

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

Opportunistic infections
Patients receiving [HA644 trade name] or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by heath care providers experienced in the treatment of these associated HIV diseases.

Liver disease
Caution should be exercised when administering lamivudine to any patient with hepatitis B coinfection. Lamivudine is an inhibitor of hepatitis B virus (HBV) replication. Discontinuation of lamivudine or virologic failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. Periodic monitoring of liver function tests and markers of HBV replication is recommended for at least four months if lamivudine is discontinued in HBV-coinfected patients.

Patients with chronic hepatitis B or C and 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 refer also to the relevant product information for these medicinal products.

If [HA644 trade name] is discontinued in patients co-infected 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 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 (see section 4.8).

Paediatric population
In a study performed in paediatric patients (see section 5.1), lower rates of virologic suppression and more frequent viral resistance were reported in children receiving lamivudine oral solution as compared to those receiving the tablet formulation. Whenever possible in children, lamivudine as tablet formulation should preferably be used.

Osteonecrosis
Cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy. Their etiology 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.

Drug Interactions
[HA644 trade name] should not be taken with any other medicinal product containing lamivudine.

Because of overlapping resistance and lack of additive antiretroviral effects, [HA644 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.

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.
Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolised by this system (e.g. PIs) 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 Pneumocystis jirovecii pneumonitis treatment).

Medicinal products, whose main route of elimination is active renal secretion via the organic cationic transport system, e.g. trimethoprim, may interact with lamivudine. Medicinal products (e.g. ranitidine, cimetidine), which are eliminated only in part by this mechanism, were shown not to interact with lamivudine.

Due to similarities, [HA644 trade name] should not be administered concomitantly with other cytidine analogues, such as emtricitabine. Moreover, [HA644 trade name] should not be taken with any other medicinal products containing lamivudine (see section 4.4).

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).

Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution 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 in adults. When possible, chronic coadministration of lamivudine with medicinal products containing sorbitol or other osmotic acting polyalcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol) should be avoided. More frequent monitoring of HIV-1 viral load, when chronic coadministration cannot be avoided, should be considered.

4.6 Fertility, pregnancy and breast-feeding

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).

Breast-feeding
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 [HA644 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

System organ class	Common	Uncommon	Rare	Very Rare
Blood and lymphatic system orders		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 enzymes (AST, ALT)	Hepatitis	
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 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 professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

No specific symptoms and 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 evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary. Since lamivudine is dialyzable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: nucleoside and nucleotide reverse transciptase 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 ≤ 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

Absorption of Lamivudine 150mg tablets
The absorption characteristics of Lamivudine 150mg tablets have been determined after administration of 2 tablets in healthy volunteers in the fasting state as follows:

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)
t_{max} (h)	1.10 ± 0.71	1.01 ± 0.65
C_{max} (µg/ml)	2657 ± 915 (2515)	2832 ± 981 (2675)

* geometric mean

AUC_{0-t} (µg.h/ml)	10953 ± 3123 (10579)	11368 ± 3087 (10957)
AUC_{0-inf} (µg.h/ml)	11280 ± 3161 (10908)	11698 ± 3058 (11306)

Pharmacokinetics of Lamivudine

	Lamivudine
Absorption	
Oral bioavailability	80-85%
Food effect	not clinically relevant
Distribution	
Volume of distribution (mean)	1.3 L/kg
Plasma proteinbinding*in vitro*	< 36%
Metabolism	
	Only minor route (< 10%)
Active metabolite(s)	NA*
Elimination	
Elimination half life	5-7 h 22 h for intracellular lamivudine triphosphate
Mean systemic clearance (Cl/F)	0.32 L/h/kg
% of dose excreted in urine	> 70% [predominantly cleared unchanged]
Pharmacokinetic linearity	Linear pharmacokinetics
Drug interactions *(in vitro*)	
Transporters	OCT (organic cationic transporters)

*Information not available

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. The clinical relevance of this finding is unknown.

Pharmacokinetics in children

A clinical trial in South Africa in 123 treatment-naïve, HIV-1-infected children aged 3 months to 16 years treated with nevirapine in combination with zidovudine and lamivudine indicated that either the weight-based or the body surface area-based dosing produced nevirapine plasma concentrations

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.

Mutagenecity and carcinogenecity
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, magnesium stearate
Film coat: Hypromellose, polyethylene glycol, polysorbate, titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

Store tablets in blisters in the provided carton.

6.5 Nature and contents of container

Blister packs
Blister strips of PVDC coated PVC film and plain aluminium foil containing 10 tablets. The blisters strips are placed in one outer carton box (6 strips per box).

HDPE bottle packs
Round opaque white coloured open mouth HDPE bottle with polypropylene child resistant caps containing 60 tablets.

6.6 Instructions for use and handling and disposal

No special requirements.

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 (PREQUALIFICATION PROGRAMME)

HA644

9. DATE OF FIRST PREQUALIFICATION

26 October 2016

10. DATE OF REVISION OF THE TEXT

November 2019

Detailed information on this medicinal product is available on the website of the WHO Prequalification Programme https://extranet.who.int/prequal

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 2016 - 2nd ed., available at: http://www.who.int/hiv/pub/arv/arv-2016/en/

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