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

[HA743 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains abacavir (as sulfate) 600 mg and lamivudine 300 mg.

Excipients with potential clinical effect

Each tablet contains 0.848 mg FD&C yellow #6/sunset yellow FCF aluminium lake.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Orange, capsule-shaped, biconvex (rounded on top and bottom), film-coated tablet, debossed (stamped into) with 'C' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA743 trade name] is indicated as part of antiretroviral combination therapy for the treatment of HIV infection in adults, adolescents and children weighing at least 25 kg.

Because [HA743 trade name] contains abacavir, patients must be screened for HLA-B*5701 (a variant form of a gene) and [HA743 trade name] must not be used in patients who carry it (see section 4.4).

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

4.2 Posology and method of administration

Oral use.

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

Posology

Adults, adolescents and children weighing at least 25 kg:

The recommended dose of [HA743 trade name] is one tablet once daily.

Children under 25 kg

[HA743 trade name] is not suitable for children weighing less than 25 kg. For these patients another formulation containing lower amounts of abacavir and lamivudine should be used.

Dose adjustment

[HA743 trade name] should not be prescribed for patients requiring dosage adjustments. Separate formulations of abacavir or lamivudine should be used if it is necessary to discontinue or adjust the dose of one of the active substances.

Special Populations

Elderly

No pharmacokinetic data are currently available in patients over 65 years of age. Special care is advised in the elderly due to age-associated changes such as impaired renal function and alteration of haematological parameters.

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

Renal impairment

[HA743 trade name] is not recommended in patients whose creatinine clearance is less than 30 mL/minute (see section 5.2), as appropriate dose adjustments cannot be made.

Hepatic impairment:

Abacavir is primarily metabolised by the liver. No data are available in patients with moderate or severe hepatic impairment; therefore, [HA743 trade name] is not recommended unless the benefits are considered to outweigh the risks. In patients with mild hepatic impairment close monitoring is required (see sections 4.4 and 5.2).

Missed dose

If a dose is missed and this is noticed within 12 hours (for once-daily dosing), 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

[HA743 trade name] should be taken with some water. It can be taken with food or between meals.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
[HA743 trade name] must **not** be used in patients:

- carrying the variant gene allele HLA-B*5701
- who have already had or are suspected to have had abacavir-associated hypersensitivity reactions (see section 4.8)

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Abacavir is associated with serious hypersensitivity reactions (see section 4.8) characterised by fever or rash or both with other symptoms indicating multi-organ involvement. Some hypersensitivity reactions with abacavir have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for abacavir hypersensitivity reactions is high for patients that have the HLA-B*5701 allele (variant gene). However, abacavir hypersensitivity reactions have also been reported at a lower frequency in patients who do not carry this allele.

Therefore:

- HLA-B*5701 status must **always** be determined before starting [HA743 trade name].
- [HA743 trade name] must **never** be started in patients who are positive for HLA-B*5701, nor in patients negative for HLA-B*5701 but who had a suspected hypersensitivity reaction on a previous abacavir-containing regimen. [HA743 trade name] **must be stopped at once**, even in the absence of the HLA-B*5701 allele, if a hypersensitivity reaction is suspected. Delay in stopping [HA743 trade name] treatment after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with [HA743 trade name] for a suspected hypersensitivity reaction, the patient must **never** be given [HA743 trade name] or any other medicine containing abacavir.
- Restarting an abacavir-containing medicine after a hypersensitivity reaction to abacavir can cause swift return of symptoms within hours. This recurrence is usually more severe than the previous reaction and may include life-threatening hypotension and death.
- To prevent accidental use of abacavir, patients who had a suspected hypersensitivity reaction should be instructed to dispose of all remaining [HA743 trade name].

Rarely, patients who stopped abacavir for reasons other than symptoms of hypersensitivity reaction have also suffered life-threatening reactions within hours of restarting abacavir. In such patients, abacavir must be restarted in a setting where medical assistance is readily available.

Description of abacavir hypersensitivity reactions

Abacavir hypersensitivity reactions have been well characterised through clinical studies and post-marketing follow-up. Symptoms usually appeared within the first 6 weeks (median time to onset 11 days) of starting abacavir treatment, but they **may occur at any time during therapy**.

Almost all abacavir hypersensitivity reactions include fever or rash. Other signs and symptoms that occur as part of the hypersensitivity reactions are detailed in section 4.8 (under 'Abacavir hypersensitivity'); they include respiratory and gastrointestinal symptoms. Importantly, such symptoms **may be mistaken for respiratory disease** (pneumonia, bronchitis, pharyngitis) **or gastroenteritis.**

The symptoms of hypersensitivity reactions resolve on discontinuing abacavir but worsen with continued therapy.

Other warnings and precautions

Mitochondrial dysfunction following exposure in utero

Nucleoside analogues such as abacavir and lamivudine may cause a variable degree of mitochondrial damage. Mitochondrial dysfunction has been reported 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, hyperlipasaemia). 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 who has been exposed in utero to nucleoside and nucleotide analogues and who presents with severe clinical findings of unknown aetiology, particularly neurological defects. 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 blood lipids and glucose. Lipid disorders should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported, but it is uncertain if abacavir or lamivudine treatment causes it.

If signs, symptoms or laboratory abnormalities for pancreatitis occur then management of pancreatitis would include the substitution with another therapeutic class.

Risk of virological failure

A high rate of virological failure, and of emergence of resistance have been reported at an early stage when abacavir and lamivudine were combined with tenofovir disoproxil (triple nucleoside therapy) as a once-daily regimen.

The risk of virological failure with [HA743 trade name] might be higher than with other therapeutic options (see section 5.1).

Liver disease

The safety and efficacy of [HA743 trade name] has not been established in patients with significant liver disorders. [HA743 trade name] is not recommended in patients with moderate or severe hepatic impairment (see section 5.2).

Patients with liver dysfunction, including chronic active hepatitis, have a higher frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored. If liver disease worsens in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with chronic hepatitis B or C virus

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. Product information for antiviral medicines for treating hepatitis B or C may include further information.

If [HA743 trade name] is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of hepatitis B virus replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Cardiovacular events

Observational studies suggest an increased risk of cardiovascular events such as myocardial infarction in patients treated with abacavir. When prescribing [HA743 trade name], action should be taken to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Alternative treatment options to the abacavir containing regimen should be considered when treating patients with a high cardiovascular risk.

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.

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 speak with their health care provider about joint aches and pain, joint stiffness or movement difficulty.

Opportunistic infections

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

Administration in subjects with moderate renal impairment

Adult patients with a creatinine clearance between 30 and 49 mL/min receiving [HA743 trade name] may experience a 1.6-to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomised, controlled trials comparing [HA743 trade name] to the individual components in adults with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in <1% of subjects. Other lamivudine-related adverse events (such as gastro-intestinal and hepatic disorders) may occur.

Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive [HA743 trade name] should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, as per lamivudine prescribing information, is indicated, which cannot be achieved with [HA743 trade name]. [HA743 trade name] should be discontinued, and the individual components should be used to construct the treatment regimen.

4.5 Interaction with other medicinal products and other forms of interaction

[HA743 trade name] contains abacavir and lamivudine, therefore any interactions identified for these individually may occur with [HA743 trade name]. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine.

Abacavir is metabolised by UDP-glucuronyltransferase (UGT) enzymes and alcohol dehydrogenase; co-administration of inducers or inhibitors of UGT enzymes or with compounds eliminated through alcohol dehydrogenase could alter abacavir exposure.

Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through organic cation transporters (OCTs); co-administration of lamivudine with OCT inhibitors may increase lamivudine exposure.

Abacavir and lamivudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) nor do they induce this enzyme system. Lamivudine does not inhibit cytochrome P450 enzymes. Abacavir shows limited potential to inhibit CYP3A4-mediated metabolism and has been shown in vitro not to inhibit CYP2C9 or CYP2D6 enzymes. In vitro studies have shown that abacavir has potential to inhibit cytochrome P450 1A1 (CYP1A1). Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicines metabolised by major P450 enzymes.

[HA743 trade name] should not be taken with any other medicines that containing lamivudine.

The list below should not be considered exhaustive but is representative of the classes studied.

Interacting drugs	**Interaction** **Geometric mean change (%)** **(Possible mechanism)**	**Recommendation on co-administration**
Antiretroviral medicines		
Didanosine with abacavir	Interaction not studied.	No dose adjustment necessary.
Didanosine with lamivudine	Interaction not studied.	
Zidovudine with abacavir	Interaction not studied	
Zidovudine with lamivudine Zidovudine 300 mg single dose Lamivudine 150 mg single dose	Lamivudine: AUC ↔ Zidovudine: AUC ↔	
Emtricitabine with lamivudine		Due to similarities, [HA743 trade name] should not be administered concomitantly with other cytidine analogues, such as emtricitabine.
Tipranavir/lamivudine with abacavir	Plasma concentration of abacavir significantly reduced	Co-administration of [HA743 trade name] with tipranavir/ritonavir is not recommended unless other nucleoside reverse transcriptase inhibitors cannot be used
Anti-infective medicines		
Trimethoprim/sulfamethoxazole with abacavir	Interaction not studied.	No [HA743 trade name] dose adjustment necessary.
Trimethoprim/sulfamethoxazole with lamivudine Trimethoprim/sulfamethoxazole 160 mg/800 mg once daily for 5 days Lamivudine300 mg single dose	Lamivudine: AUC ↑ 40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	When co-administration with trimethoprim/sulfamethoxazole is necessary, patients should be monitored clinically. High doses of trimethoprim/sulfamethoxazole for treating *Pneumocystis jirovecii* pneumonia (PCP) and of toxoplasmosis have not been studied and should be avoided

Interacting drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation on co-administration
Flucytosine with lamivudine	Potential for haematological toxicity	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.
Antimycobacterials		
Rifampicin with abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dose adjustment.
Rifampicin with lamivudine	Interaction not studied.	
Anticonvulsants		
Phenobarbital with abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dose adjustment.
Phenobarbital with lamivudine	Interaction not studied.	
Phenytoin with abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dose adjustment. Monitor phenytoin concentrations.
Phenytoin with lamivudine	Interaction not studied.	
Antihistamines (histamine H2 receptor antagonists)		
Ranitidine with abacavir	Interaction not studied.	No dose adjustment necessary.
Ranitidine with lamivudine	Interaction not studied. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	
Cimetidine with abacavir	Interaction not studied.	No dosage adjustment necessary.
Cimetidine with lamivudine	Interaction not studied. Clinically significant interaction unlikely. Cimetidine eliminated only in part by renal organic cation transport system.	
Cytotoxics		
Cladribine with lamivudine	Interaction not studied. In vitro, lamivudine inhibits intracellular phosphorylation of cladribine, leading to a potential risk of reduced cladribine efficacy. Some clinical findings also support a possible interaction between lamivudine and cladribine	Concomitant use of lamivudine with cladribine is not recommended.

Interacting drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation on co-administration
Cisplatin with lamivudine	Cisplatin and lamivudine could potentially compete for OCT2 which could slow their elimination. Also, cisplatin may impair renal function	Renal function should be monitored.
Opioids		
Methadone with abacavir Methadone 40–90 mg once daily for 14 days Abacavir 600 mg single dose, then 600 mg twice daily for 14 days	Abacavir: AUC ↔ C_{max} ↓ 35% Methadone: CL/F ↑ 22%	No [HA743 trade name] dose adjustment necessary. Methadone dose adjustment unlikely to be needed in most patients; occasionally methadone re-titration may be required.
Methadone/Lamivudine	Interaction not studied.	
Retinoids		
Retinoid compounds (e.g. isotretinoin) with abacavir	Interaction not studied. Possible interaction given common pathway of elimination via alcohol dehydrogenase.	Insufficient data to recommend dose adjustment.
Retinoid compounds (e.g. isotretinoin) with lamivudine	Interaction not studied.	
Miscellaneous		
Ethanol with abacavir Ethanol 700 mg/kg single dose Abacavir 600 mg single dose	Abacavir: AUC ↑41% Ethanol: AUC ↔ (Inhibition of alcohol dehydrogenase)	No dose adjustment necessary.
Ethanol with lamivudine	Interaction not studied.	
Sorbitol with lamivudine Sorbitol solution (3.2 g, 10.2 g, 13.4 g) Lamivudine oral solution 300 mg single dose	Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic co-administration of [HA743 trade name] with medicines containing sorbitol or other osmotic-acting poly-alcohols or monosaccharide alcohols (e.g. lactitol, maltitol, mannitol and xylitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.
Riociguat with abacavir	Riociguat ↑ In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving abacavir/dolutegravir/lamivudine (600 mg/50 mg/300 mg once daily) led to about 3-fold higher riociguat AUC compared to historical riociguat AUC in healthy subjects.	Riociguat dose may need to be reduced. Consult the riociguat prescribing information for dosing recommendations.
Clopidrogrel with abacavir	Pharmacodynamic effect of clopidogrel maybe reduced.	An alternative NRTI or antiplatelet agent should be considered.

Interacting drugs	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation on co-administration

↓	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)

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and breast-feeding

Pregnancy

Studies of abacavir and lamivudine in animals have shown reproductive toxicity (see section 5.3).

No increased birth defects have been reported for abacavir or lamivudine in humans. However, placental transfer of abacavir and lamivudine can occur.

If a patient becomes pregnant during treatment, [HA743 trade name] may be continued if the benefit is considered to outweigh the risk. However, [HA743 trade name] should **not be started** during pregnancy, due to the risk of a hypersensitivity reaction to abacavir.

Patients co-infected with hepatitis and being treated with lamivudine containing medicinal products such as [HA743 trade name] and who becomes pregnant may be subject to recurrence of hepatitis on discontinuation of [HA743 trade name].

Mitochondrial dysfunction

In vitro and in vivo studies show that nucleoside and nucleotide analogues such as abacavir and lamivudine cause a variable degree of mitochondrial damage. Mitochondrial dysfunction has been reported in HIV-negative infants exposed to nucleoside analogues in utero or after birth (see section 4.4).

Breast-feeding

Abacavir and lamivudine are present in breast milk.

Current recommendations on HIV and breast-feeding (e.g. those from the WHO) should be followed to advise patients on breast-feeding. Preferred options may vary depending on the local circumstances.

Fertility

Studies in animals showed that neither abacavir nor lamivudine had any effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

[HA743 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions reported are consistent with those of abacavir and lamivudine given separately. It is unclear whether many of these adverse reactions are related to the active substance, the wide range of other medicines used to manage HIV infection, or whether they result from the underlying disease.

Many of the adverse reactions listed below occur commonly (nausea, vomiting, diarrhoea, fever, lethargy, rash) in patients with abacavir hypersensitivity— see ‘Abacavir hypersensitivity’, below. Therefore, patients with any of these symptoms should be carefully evaluated for hypersensitivity.

Very rarely cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicines containing abacavir should be permanently discontinued.

Tabulated list of adverse reactions

The adverse reactions considered at least possibly related to abacavir or lamivudine are listed below. Frequencies are defined as very common (more than 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1/10 000 to 1 in 1000), and very rare (less than 1 in 10 000).

Blood and lymphatic systems disorders	
Uncommon	neutropenia and anaemia (both occasionally severe), thrombocytopenia
Very rare	pure red cell aplasia
Immune system disorders	
Common	Hypersensitivity (see 'Abacavir hypersensitivity', below)
Metabolism and nutrition disorders	
Common	anorexia
Very rare	lactic acidosis
Nervous system disorders	
Common	headache, insomnia
Very rare	peripheral neuropathy (or paraesthesia)
Respiratory, thoracic and mediastinal disorders	
Common	cough, nasal symptoms
Gastrointestinal disorders	
Common	nausea, vomiting, abdominal pain or cramps, diarrhoea
Rare	pancreatitis, but causal relationship to abacavir treatment uncertain rises in serum amylase
Hepatobiliary disorders	
Uncommon	transient rises in liver enzymes (AST, ALT)
Rare	hepatitis
Skin and subcutaneous tissue disorders	
Common	rash (without systemic symptoms), alopecia
Rare	angioedema
Very rare	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Common	arthralgia, muscle disorders
Rare	rhabdomyolysis
General disorders and administration site conditions	
Common	fever, lethargy, malaise, fatigue

Abacavir hypersensitivity

The signs and symptoms of abacavir hypersensitivity are listed below. They have been identified from clinical studies and post marketing surveillance. Those reported in at least 10% of patients with a hypersensitivity reaction are shown in **bold**.

Almost all patients developing hypersensitivity reactions had fever or rash (usually maculopapular or urticarial) as part of the syndrome; however, reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract	**Nausea, vomiting, diarrhoea, abdominal pain**, mouth ulceration
Respiratory tract	**Dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous	**Fever, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry	**Headache**, paraesthesia
Haematological	Lymphopenia
Liver	**Elevated liver function tests,** hepatitis, hepatic failure
Musculoskeletal	**Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology	Elevated creatinine, renal failure

Symptoms related to abacavir hypersensitivity worsen with continued therapy and can be life- threatening and in rare instances, fatal.

Restarting abacavir after an abacavir hypersensitivity reaction may result in a return of symptoms within hours. This recurrence of the hypersensitivity reactions is usually more severe than on initial presentation and may include life-threatening hypotension and death. Similar reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) before stopping abacavir; and on very rare occasions hypersensitivity reactions have occurred in patients who restarted therapy with no preceding symptoms of hypersensitivity reactions (i.e. patients previously considered to be abacavir tolerant).

See also section 4.4 for metabolic parameter, immune reactivation syndrome and osteonecrosis.

Children and adolescents

No additional safety issues have been identified in paediatric subjects receiving abacavir and lamivudine either once or twice daily. This is based on data from 669 HIV-infected patients aged from 1 up to 17 years receiving abacavir and lamivudine either once or twice daily.

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 abacavir or lamivudine, apart from those listed as undesirable effects. An important feature of toxicity may be mitochondrial damage, which can result in disorders such as lactic acidosis.

If overdose occurs the patient should be monitored for toxicity (see section 4.8) and receive standard supportive treatment as necessary. Since lamivudine is dialysable, continuous haemodialysis may be used to treat an overdose, but this has not been studied. It is not known if abacavir can be removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations,
ATC code: J05AR02

Mechanism of action

Abacavir and lamivudine are nucleoside analogue reverse transcriptase inhibitors (NRTIs). Both are metabolised sequentially by intracellular kinases to the respective 5′-triphosphate (TP) active forms. Carbovir-TP (the active triphosphate form of abacavir) and lamivudine-TP competitively inhibit the reverse transcriptase (RT) of HIV. Abacavir and lamivudine triphosphates have significantly less affinity for host cell DNA polymerases.

Clinical efficacy

Adults

Abacavir and lamivudine tablets was shown to be effective against HIV in three main studies involving a total of 1,230 patients. Abacavir was authorised at a dose of 300 mg twice a day. Studies were done where abacavir taken at a dose of 600 mg once a day and at a dose of 300 mg twice a day, in combination with lamivudine and one or two other antiviral medicines were compared. The main measure of effectiveness was the change in the level of HIV in the blood (viral load) after 24 or 48 weeks of treatment.

Two studies used the active substances, abacavir and lamivudine, taken as separate medicines. Both doses of abacavir, taken in combination with lamivudine and other antiviral medicines, were equally effective in reducing viral loads. In the first study, 66% (253 out of 384) of the patients taking abacavir once a day had undetectable viral loads (below 50 copies/mL) after 48 weeks of treatment, compared with 68% (261 out of 386) of the patients taking it twice a day.

The third study used a combination tablet for the once-daily dose. The combination tablet taken once a day was as effective as the medicines taken separately twice a day in reducing viral loads over 24 weeks of treatment.

Children

Among 45 antiretroviral therapy-naïve children aged 3 months to 16 years receiving abacavir/lamivudine in combination with nelfinavir (except 6 who received only abacavir/lamivudine) 56% had viral load less than 50 copies after 48 weeks of treatment.

In a study in 669 patients aged 1 to under 17 years, abacavir/lamivudine once daily had similar efficacy to giving it twice daily.

Resistance

Clinically significant reduction of susceptibility to abacavir has occurred in patients with uncontrolled viral replication, who were resistant to other nucleoside inhibitors. In clinical trials where abacavir was added to the antiretroviral regimen, patients had M184V/I (74%), T215Y/F (30%), M41L (27%), K70R (18%) and D67N (15%). Variants L74V and Y115F were uncommon (no more than 3%). It was considered that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at week 4, or 4 or more mutations at week 24. In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, causes a high level of resistance to abacavir.

Resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple thymidine analogue mutations. Cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir remain active against such HIV-1 variants. M184V with K65R confers cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. M184V with Y115F confers cross-resistance between abacavir and lamivudine.

Isolates resistant to abacavir may also show reduced sensitivity to lamivudine. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, and to viruses with L74V plus the M184V/I substitution. The M184V or M184I variants arise in patients treated with lamivudine-containing antiretroviral therapy and confer high-level resistance to lamivudine. Laboratory data suggest that continuing lamivudine despite the development of M184V might provide residual antiretroviral activity. However, the clinical relevance of these findings

has not been established, and the patient should preferably be switched to NRTIs that the HIV is susceptible to lamivudine may be continued only if no other active NRTI is available.

Appropriate use of abacavir and lamivudine can be guided by using recommended resistance algorithms. Cross-resistance between abacavir or lamivudine and antiretrovirals from other classes e.g. PIs or NNRTIs is unlikely.

5.2 Pharmacokinetic properties

Absorption of [HA743 trade name]

The absorption characteristics of [HA743 trade name] have been determined after administration of a single dose tablet in healthy volunteers under fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean ±standard deviation**	
	Abacavir	**Lamivudine**
Time to attain maximum concentration T_{max} (h)	1.82 ± 0.58	2.62 ± 0.74
Maximum concentration C_{max} (ng/mL)	6190 ± 1328	3021 ± 827
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption (ng·h/mL)	19293 ± 4387	16439 ± 3932

Pharmacokinetics of abacavir and lamivudine

	Abacavir	**Lamivudine**
General	NA*	NA*
Absorption		
Absolute bioavailability	83%	NA*
Oral bioavailability	At least 83%	80–85%
Food effect	Concomitant food intake did not affect the extent of absorption but increased T_{max} and decreased C_{max}	Not clinically relevant
Distribution		
Volume of distribution (mean)	0.8 L/kg	1.3 L/kg
Plasma proteinbinding *in vitro*	About 49% (binding to human plasma proteins)	< 36%
Tissue distribution	CSF to plasma AUC ratio: 30 to 44%	
Metabolism		
	hepatic metabolism followed by glucuronidation to produce 5'-carboxylic acid and 5'-glucuronide	Only minor route (< 10%)
Active metabolite(s)	None	None
Elimination		
Elimination half life	1.5 hours after single dose 21 hours for intracellular carbovir triphosphate	18–19 hours 16–19 hours for intracellular lamivudine triphosphate
Mean systemic clearance (Cl/F)	NA*	0.32 L/hour/kg.
% of dose excreted in urine	Approximately 2% excreted unchanged; total 83%	> 70% (predominantly cleared unchanged)

% of dose excreted in faeces	16%	NA*
Pharmacokinetic linearity	Linear pharmacokinetics and dose proportional over the range of 300–1200 mg/day	Linear pharmacokinetics
Drug interactions (in vitro)		
Transporters	NA*	OCT (organic cationic transporters)
Metabolising Enzymes	Alcohol dehydrogenase, UDP-glucuronyltransferase	-

NA* = Information not available

Special populations

Hepatic impairment

Pharmacokinetic data has been obtained for abacavir and lamivudine alone.

Abacavir is metabolised primarily by the liver. In patients with mild hepatic impairment (Child-Pugh score 5–6) receiving a single 600-mg dose, there was a mean 1.89-fold increase in the abacavir AUC, and 1.58-fold increase in the elimination half-life. No recommendation on dose adjustments can be made for these patients due to the substantial variability of abacavir exposure.

Data from patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

[HA743 trade name] is not recommended in patients with moderate or severe hepatic impairment.

Renal impairment

Pharmacokinetic data have been obtained for lamivudine and abacavir alone.

Abacavir is primarily metabolised by the liver, with about 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function.

Lamivudine plasma concentrations are increased in patients with renal dysfunction due to decreased clearance.

[HA743 trade name] is not recommended in patients with a creatinine clearance less than 30 mL/minute because necessary dose adjustments cannot be made.

Children

Abacavir is rapidly and well absorbed from oral formulations when administered to children. Paediatric pharmacokinetic studies have demonstrated that once-daily dosing provides equivalent AUC_{24} to twice-daily dosing of the same total daily dose for both oral solution and tablet formulations.

The absolute bioavailability of lamivudine (about 58 to 66%) was lower and more variable in children under 12 years of age. However, paediatric pharmacokinetic studies with tablet formulations have demonstrated that once-daily dosing provides equivalent $AUC_{0\text{-}24h}$ to twice-daily dosing of the same total daily dose.

Elderly

No pharmacokinetic data are available in patients over 65 years of age.

5.3 Preclinical safety data

With the exception of a negative in vivo rat micronucleus test, there is no data available on the effects of the combination of abacavir and lamivudine in animals.

General toxicity

In toxicology studies abacavir increased liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, autoinduction of abacavir metabolism, or induction of the metabolism of other medicines metabolised in the liver has not been seen in humans.

Mild myocardial degeneration occurred in mice and rats after administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

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. Clinically relevant effects were a reduction in red blood cell count and neutropenia.

Mutagenicity and carcinogenicity

Abacavir and lamivudine 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. Based on available data, lamivudine should not pose a genotoxic hazard to patients. Abacavir has a weak potential to cause chromosomal damage both in vitro and in vivo at high tested concentrations.

The carcinogenic potential of a combination of abacavir and lamivudine has not been tested.

The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential. Carcinogenicity studies with oral abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and in the liver, urinary bladder, lymph nodes and the subcutis of females.

Most of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no-effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. 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

Abacavir and lamivudine crossed the placenta in animal studies.

Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryo lethality at systemic exposure similar to the recommended clinical dose. A similar effect was not seen in rats even at very high systemic exposure.

Abacavir was toxic to the developing embryo and fetus in rats, but not in rabbits. These findings included decreased fetal body weight, fetal oedema, increased skeletal variations or malformations, early intra-uterine deaths and stillbirths. No conclusion can be drawn about the teratogenic potential of abacavir because of this embryo-fetal toxicity.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: microcrystalline cellulose

sodium starch glycolate
hypromellose
corn starch
colloidal silicon dioxide
magnesium stearate

Film coat: hypromellose
titanium dioxide
FD&C yellow #6/sunset yellow FCF aluminium lake
macrogol/polyethylene glycol
polysorbate 80

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
24 months

6.4 Special precautions for storage
Do not store above 30°C

6.5 Nature and contents of container
White HDPE container with 1g silica gel bag containing 30 tablets. The closures are either white non-child resistant HDPE, white polypropylene child resistant or blue polypropylene child resistant caps

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed off in accordance with local requirements

7. SUPPLIER
Cipla Ltd.
Cipla House
Peninsula Business Park
Ganpatrao Kadam Marg
Lower Parel
Mumbai: 400013
India
Tel.: 91 22 4191 6000
Fax: 91 22 4191 6120

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)
HA743

9. DATE OF PREQUALIFICATION
10 March 2023

10. DATE OF REVISION OF THE TEXT

June 2026

References

General

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240031593, accessed March 2026)

Guidelines for HIV post-exposure prophylaxis, 2024 (https://iris.who.int/bitstream/handle/10665/378221/9789240095137-eng.pdf, accessed 22 March 2026)

Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: Interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018 (WHO/CDS/HIV/18.51;https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1, accessed 7 June 2023).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed.. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/208825, accessed 22 March 2026).

Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240052390, accessed 7 June 2023).

Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B Infection 2024 (https://iris.who.int/bitstream/handle/10665/376353/9789240090903-eng.pdf)

Kivexa 600 mg/300 mg film-coated tablets: summary of product characteristics. European Medicines Agency; 19 January 2026 (https://www.ema.europa.eu/en/documents/product-information/kivexa-epar-product-information_en.pdf, accessed 22 March 2026).

Section 4.5

Aptivus 250 mg soft capsules: summary of product characteristics. European Medicines Agency; 23 August 2022 (https://www.ema.europa.eu/en/documents/product-information/aptivus-epar-product-information_en.pdf, accessed 13 June 2023)

HIV drug interactions: interactions checker [online database]. Liverpool Drug Interactions Group, University of Liverpool; 2023 (https://hiv-druginteractions.org/checker, accessed 13 June 2023).

Sections 4.6 and 5.3

Drugs and lactation database [online database]. Bethesda: National Institute of Child Health and Human Development; 2023 (https://www.ncbi.nlm.nih.gov/books/NBK501922, accessed 13 June 2023).

Reprotox [online database]. Apple Valley (Minnesota): Reproductive Toxicology Center; 2023. Available from: https://reprotox.org Registration and login required.

World Health Organization, United Nations Children's Fund. Guideline: updates on HIV and infant feeding: the duration of breastfeeding, and support from health services to improve feeding practices among mothers living with HIV. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/246260/9789241549707-eng.pdf, accessed 13 June 2023)

Section 4.9

van Dam PM, van Geffen MW, Havenith TR, Posthouwer D. Intentional overdose of dolutegravir/abacavir/lamivudine (Triumeq) in a 26-year-old man. Antivir Ther. 2018;23:549–552. doi:10.3851/IMP3229.

Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. Lancet 2002;359:733–40. doi:10.1016/S0140-6736(02)07874-1

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products