1. NAME OF THE MEDICINAL PRODUCT

Abacavir / Lamivudine Dispersible Tablets 120 mg / 60 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 120 mg abacavir (as sulfate) and 60 mg lamivudine.
For the list of excipients, see section 6-1.

3. PHARMACEUTICAL FORM

Dispersible tablets.

White to off-white coloured, oval-shaped, biconvex, uncoated dispersible tablets, scored on one side, debossed with '8' on one half and '0' on the other half, and score line on the other side.

The tablet can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA763 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in children weighing at least 3 to 25 kg. See also section 4.4 concerning [HA763 trade name] use and HLA-B*5701 screening.

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

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

Posology

Twice-daily dosing for infants and children four weeks and older

Weight	Morning Dose	Evening dose
3 – less than 6 kg	½ tablet (60 mg /30 mg)	½ tablet (60 mg /30 mg)
6 – less than 10 kg	½ tablet (60 mg/30 mg)	1 tablet (120 mg /60 mg)
10 – less than 14 kg	1 tablet (120 mg /60 mg)	1 tablet (120 mg /60 mg)
14 – less than 20 kg	1 tablet (120 mg /60 mg)	1 ½ tablets (180 mg /90 mg)
20 – less than 25 kg	1 ½ tablets (180 mg /90 mg)	1 ½ tablets (180 mg /90 mg)

Once-daily dosing for infants and children four weeks and older

Weight	Dose
3 – less than 6 kg	1 tablet (120 mg /60 mg)
6 – less than 10 kg	1.5 tablets

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

	(180 mg /90 mg)
10 – less than 14 kg	2 tablets (240 mg /120 mg)
14 – less than 20 kg	2.5 tablets (300 mg /150 mg)
20 – less than 25 kg	3 tablets (360 mg /180 mg)

Patients weighing above 25 kg:

[HA763 trade name] should not be administered to patients who weigh more than 25 kg because appropriate dose adjustments cannot be achieved with this product.

Special Populations

Elderly:

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

Dose adjustments:

[HA763 trade name] is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments. Separate formulations of abacavir or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated.

Renal impairment:

[HA763 trade name] is not recommended for use in patients with a creatinine clearance < 50 ml/min (see section 5.2), as appropriate dose adjustments cannot be made.

Hepatic impairment:

No data are available in patients with moderate or severe hepatic impairment, therefore the use of [HA763 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 it should be taken as soon as it is noted. If the next dose is due in less than 6 hours, the forgotten dose should be skipped and the next regular dose taken when it is due. The patient should not take a double dose to make up for a missed dose.

Method of administration

Oral use

[HA763 trade name] can be taken with or without food.

The tablets should be dispersed in drinking water before administration of the dose. Each tablet should be dispersed in a minimum of 10 mL water; the maximum volume of water recommended for dispersion of a dose is 50 mL. The tablets can be taken with food or between meals.

Instructions for use

1. The required amount of drinking water should be taken in a small and clean cup and the required number of tablets should be added.
2. The cup should be gently swirled until tablets disperse, and the entire mixture should be given/taken immediately.
3. The cup should be rinsed with an additional 10 mL of water, which should be drunk by the patient to ensure the entire dose is taken.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. See sections 4.4 and 4.8.

4.4 Special warnings and precautions for use

The special warnings and precautions relevant to abacavir and lamivudine are included in this section.

There are no additional precautions and warnings relevant to [HA763 trade name].

Hypersensitivity reactions (see also section 4.8)

Abacavir is associated with a risk for hypersensitivity reactions (HSR) (see section 4.8) characterized by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

Therefore, the following should be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- [HA763 trade name] should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir containing regimen.

[HA763 trade name] **must be stopped without delay**, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with [HA763 trade name] after the onset of hypersensitivity may result in a life-threatening reaction.

- After stopping treatment with [HA763 trade name] for reasons of a suspected HSR, [HA763 trade name] **or any other medicinal product containing abacavir must never be re-initiated**.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation and may include life-threatening hypotension and death.
- In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining [HA763 trade name].

Clinical description of abacavir HSR

Abacavir HSR has been well characterized through clinical studies and during post marketing follow-up. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, **although these reactions may occur at any time during therapy.**

Almost all HSR to abacavir include fever or rash. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms **may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.**

The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re-initiating abacavir therapy (see section 4.8 Description of selected adverse reactions). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with zidovudine. Mitochondrial dysfunction has been reported in HIV-negative infants exposed to nucleoside analogues *in utero* or post-natally, mainly with regimens containing zidovudine. The main adverse reactions are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These reactions are often transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion and abnormal behaviour). It is not known if these neurological disorders are transient or permanent. These findings 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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. For lipids, there is evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. HIV treatment guidelines should be used for recommendations on monitoring blood lipids and glucose. Lipid disorders should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported, but a causal relationship to abacavir or lamivudine treatment is uncertain.

Risk of virological failure

- Triple nucleoside therapy: 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 fumarate as a once daily regimen.
- The risk of virological failure with [HA763 trade name] might be higher than with other therapeutic options (see section 5.1).

Liver disease

The safety and efficacy of [HA763 trade name] has not been established in patients with significant underlying liver disorders. [HA763 trade name] is not recommended in patients with moderate or severe hepatic impairment (see sections 4.2 and 5.2).

Patients with 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 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 have an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

If [HA763 trade name] is discontinued in patients co-infected with HBV, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Myocardial infarction

Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall, the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there

is no established biological mechanism to explain a potential increase in risk. When prescribing [HA763 trade name], action should be taken to minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia).

Immune Reactivation Syndrome

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

Osteonecrosis

Cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease or long-term exposure to combination antiretroviral therapy. The etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, advanced HIV disease and 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.

Opportunistic infections

Patients receiving [HA763 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 health care providers experienced in the treatment of these associated HIV diseases.

Transmission of HIV

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

Drug Interactions

[HA763 trade name] should not be taken with any other medicinal products containing lamivudine.

Because of overlapping resistance and lack of additive antiretroviral effects, [HA763 trade name] should not be co-administered with emtricitabine.

The combination of [HA763 trade name] with cladribine is not-recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

[HA763 trade name] contains abacavir and lamivudine, therefore any interactions identified for these individually may occur with [HA763 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 inhibit or induce this enzyme system. Lamivudine does not inhibit cytochrome P450 enzymes. Abacavir shows limited potential to inhibit metabolism mediated by CYP3A4 and has been shown in vitro not to inhibit CYP2C9 or CYP 2D6 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 medicinal products metabolised by major P450 enzymes.

[HA763 trade name] should not be taken with any other medicinal products containing lamivudine (see section 4.4).

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

Drugs by Therapeutic Area	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration
ANTIRETROVIRAL MEDICINAL PRODUCTS		
Didanosine /Abacavir	Interaction not studied.	No dosage adjustment necessary.
Didanosine/Lamivudine	Interaction not studied.	
Zidovudine/Abacavir	Interaction not studied	
Zidovudine/Lamivudine Zidovudine 300 mg single dose Lamivudine 150 mg single dose	Lamivudine: AUC ↔ Zidovudine: AUC ↔	
Emtricitabine/Lamivudine		Due to similarities, [HA763 trade name] should not be administered concomitantly with other cytidine analogues, such as emtricitabine.
ANTI-INFECTIVE PRODUCTS		
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Abacavir	Interaction not studied.	No [HA763 trade name] dosage adjustment necessary. When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/ sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	
ANTIMYCOBACTERIALS		
Rifampicin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Rifampicin/Lamivudine	Interaction not studied.	
ANTICONVULSANTS		
Phenobarbital/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.

Phenobarbital/Lamivudine	Interaction not studied.	
Phenytoin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment. Monitor phenytoin concentrations.
Phenytoin/Lamivudine	Interaction not studied.	

ANTIHISTAMINES (HISTAMINE H2 RECEPTOR ANTAGONISTS)		
Ranitidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
Ranitidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	
Cimetidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
Cimetidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Cimetidine eliminated only in part by renal organic cation transport system.	
CYTOTOXICS		
Cladribine/Lamivudine	Interaction not studied. *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).
OPIOIDS		
Methadone/Abacavir (40 to 90mg once daily for 14 days/600mg single dose, then 600mg twice daily for 14 days)	Abacavir: AUC ↔ C_{max} ↓35% Methadone: CL/F ↑22%	No [HA763 trade name] dosage adjustment necessary. Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration may be required.
Methadone/Lamivudine	Interaction not studied.	
RETINOIDS		

Retinoid compounds (e.g. isotretinoin)/Abacavir	Interaction not studied. Possible interaction given common pathway of elimination via alcohol dehydrogenase.	Insufficient data to recommend dosage adjustment.
Retinoid compounds (e.g. isotretinoin)/Lamivudine No drug interaction studies	Interaction not studied.	
MISCELLANEOUS		
Ethanol/Abacavir (0.7 g/kg single dose/600 mg single dose)	Abacavir: AUC ↑41% Ethanol: AUC ↔ (Inhibition of alcohol dehydrogenase)	No dosage adjustment necessary.
Ethanol/Lamivudine	Interaction not studied.	

Sorbitol solution (3.2 g, 10.2 g, 13.4 g)/ Lamivudine	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of [HA763 trade name] with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.
Riociguat/Abacavir	Riociguat ↑ In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving the combination of abacavir/dolutegravir/lamivudine (600mg/50mg/300mg once daily) led to an approximately three-fold higher riociguat $AUC_{(0-\infty)}$ when compared to historical riociguat $AUC_{(0-\infty)}$ reported in healthy subjects.	Riociguat dose may need to be reduced. Consult the riociguat prescribing information for dosing recommendations.

↓	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)

4.6 Fertility, pregnancy and breastfeeding *Pregnancy*

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

No increased risk of birth defects has been reported for abacavir or lamivudine (www.apregistry.com). However, risks to the foetus cannot be ruled out.

Abacavir / Lamivudine Dispersible Tablets 120 mg / 60 mg]can be used in pregnancy if clinically indicated. Abacavir / Lamivudine Dispersible Tablets 120 mg / 60 mg
should not be initiated during pregnancy, due to the risk of a hypersensitivity reaction to abacavir. If a patient becomes pregnant during treatment with [Abacavir / Lamivudine Dispersible Tablets 120 mg / 60 mg
], however, this abacavir- containing therapy may be continued if the benefit is considered to outweigh the risk. *Mitochondrial dysfunction*

Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV- negative infants exposed in utero and/or post-natally to nucleoside analogues (see section 4.4).

Breast-feeding

Abacavir and lamivudine are excreted into the breast milk of lactating mothers.

Current recommendations on HIV and breast-feeding (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

There are no data on the effects of Abacavir / Lamivudine Dispersible Tablets 120 mg / 60 mg
on human male or female 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

No studies are available on the effects of [HA763 trade name] on the ability to drive and use machines. Nevertheless, the clinical status of the patient and the adverse reaction profile of [HA763 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions reported for Kivexa were consistent with the known safety profiles of abacavir and lamivudine when given as separate medicinal products. For many of these adverse reactions it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process.

Many of the adverse reactions listed in the table below occur commonly (nausea, vomiting, diarrhoea, fever, lethargy, rash) in patients with abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity (see section 4.4). 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 medicinal products 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 by body system, organ class and absolute frequency. Frequencies are defined as very common (> 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to < 1/100), rare (> 1/10,000 to < 1/1000), very rare (< 1/10,000).

SOC	**Abacavir**	**Lamivudine**
Blood and lymphatic systems disorders		Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopaenia Very rare: Pure red cell aplasia
Immune system disorders	Common: hypersensitivity	
Metabolism and nutrition disorders	Common: anorexia Very rare: lactic acidosis	Very rare: lactic acidosis
Nervous system disorders	Common: headache	Common: Headache, insomnia. Very rare: Cases of peripheral neuropathy (or paraesthesia) have been reported
Respiratory, thoracic and mediastinal disorders		Common: Cough, nasal symptoms
Gastrointestinal disorders	Common: nausea, vomiting, diarrhoea Rare: pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain	Common: Nausea, vomiting, abdominal pain or cramps, diarrhoea Rare: Rises in serum amylase. Cases of pancreatitis have been reported
Hepatobiliary disorders		Uncommon: Transient rises in liver enzymes (AST, ALT), Rare: Hepatitis

Skin and subcutaneous tissue disorders	Common: rash (without systemic symptoms)	Common: Rash, alopecia Rare: Angioedema
	Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	
Musculoskeletal and connective tissue disorders		Common: Arthralgia, muscle disorders Rare: Rhabdomyolysis
General disorders and administration site conditions	Common: fever, lethargy, fatigue.	Common: fatigue, malaise, fever.

Description of selected adverse reactions

Abacavir hypersensitivity

The signs and symptoms of this HSR are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported **in at least 10%** of patients with a hypersensitivity reaction are in bold text.

Almost all patients developing hypersensitivity reactions will have fever and/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/pancreas **Elevated liver function tests,** hepatitis, hepatic failure

Musculoskeletal **Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase

Urology Elevated creatinine, renal failure

Symptoms related to this HSR worsen with continued therapy and can be life- threatening and in rare instances, have been fatal.

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR 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) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

Metabolic parameters

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

Immune reactivation syndrome

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 and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis

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

Paediatric population

The safety database to support once daily dosing in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects (from 12 months to ≤17 years old). received abacavir and lamivudine either once or twice daily (see section 5.1). Within this population, 104 HIV-1 infected paediatric subjects weighing at least 25 kg received abacavir and lamivudine as Kivexa once daily. 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

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

4.9 Overdose

No specific symptoms or signs have been identified following acute overdose with abacavir or 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 dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. It is not known whether 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 NRTIs. Both agents are metabolised sequentially by intracellular kinases to the respective carbovir-TP (the active triphosphate form of abacavir) and 5′-triphosphate (TP). Lamivudine-TP. They are competitive inhibitors of the reverse transcriptase (RT) of both HIV-1 and HIV-2. Abacavir and lamivudine show significantly less affinity for host cell DNA polymerases.

No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: didanosine, nevirapine and zidovudine). The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Clinical efficacy Adults

Clinical experience with the combination of abacavir and lamivudine as a once daily regimen is mainly based on four studies in treatment-naïve subjects and two studies in treatment-experienced subjects. In antiretroviral therapy-naïve adult patients treated with abacavir 300 mg twice daily, together with lamivudine and efavirenz, the proportion of patients with plasma HIV-1 RNA less than 50 copies/ml by Week 48 was 70%, by intention-to-treat analysis. Though the clinical benefit of abacavir has otherwise

mainly been demonstrated in combination with lamivudine and zidovudine, this triple nucleoside regimen is no longer recommended as a preferred treatment option, due to inferior efficacy compared to NNRTI- or PI-containing regimens (see section 4.4).

Children

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

A comparison of a regimen including once daily versus twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. Among the 669 virologically suppressed subjects randomized in this study (from 12 months to ≤17 years old), 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%.

Resistance

In the pivotal clinical trials, the most common mutation emerging in patients failing on abacavir containing regimens (also including lamivudine) was M184V/I. Other key mutations appearing, though more rarely, include L74V and K65R. When occurring together with M184V/I, either of these mutations substantially reduce the activity of abacavir. The presence of M184V with K65R gives rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. A further mutation selected for and reducing the activity of abacavir is Y115F. Though TAMs (M41L, D67N/G, K70R, L210W, T215F/Y, K219E/Q/N/R) are generally not selected for when failing on abacavir-containing regimens in the absence of thymidine analogues, the presence of two or more together with M184V will substantially reduce the activity of abacavir. In addition, the 69-insertion complex or the Q151M mutation cause a high level of resistance to abacavir.

When combination antiretroviral therapy comprising lamivudine fails virologically, the M184V mutation will be selected for at an early stage (particularly if the regimen does not contain a boosted PI). M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). 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. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered when the activity of the best available NRTI backbone is significantly compromised.

5.2 Pharmacokinetic properties

The absorption characteristics of [HA763 trade name] have been determined after administration of five (5) abacavir/lamuvidine 120mg /60mg tablets in healthy volunteers in the fasted state as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**	
	Abacavir	**Lamivudine**
Maximum concentration (C_{max})	8229 ± 2196 ng/mL	3062 ± 724 ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	20582 ± 4041 ng·h/mL	16890 ± 3431 ng·h/mL
Time to attain maximum concentration (T_{max})	0.88 ± 0.49 h	2.04 ± 0.94 h

*arithmetic mean

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}	Concomitant food intake did not affect the extent of absorption but increased T_{max} and decreased C_{max} by 47%
Distribution		
Volume of distribution (mean)	0.8 L/kg	1.3 L/kg
Plasma proteinbinding *in vitro*	Approximately 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	5 - 7 hours 22 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 300-1200mg/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:

There are no data available on the use of [HA763 trade name] in hepatically impaired patients. Pharmacokinetic data has been obtained for abacavir and lamivudine alone.

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. The results showed that there was a mean increase of 1.89-fold in the abacavir AUC, and 1.58-fold in the elimination half-life. No recommendation on dosage adjustments can be given for this patient population due to the substantial variability of abacavir exposure.

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

Renal impairment:

Pharmacokinetic data have been obtained for lamivudine and abacavir alone. Abacavir is primarily metabolised by the liver with approximately 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. Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. [HA763 trade name] is not recommended for use in patients with a creatinine clearance < 50 ml/min as necessary dose adjustment 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 AUC24 to twice daily dosing of the same total daily dose for both oral solution and tablet formulations.

The absolute bioavailability of lamivudine (approximately 58 to 66%) was lower and more variable in paediatric patients under 12 years of age. However, paediatric pharmacokinetic studies with tablet formulations have demonstrated that once daily dosing provides equivalent AUC24 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 *General toxicity*

In toxicology studies abacavir was shown to increase 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 medicinal products hepatically metabolised has not been observed in man.

Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for two 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. 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. 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 orally administered 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

In reproductive toxicity studies in animals, abacavir and lamivudine were shown to cross the placenta.

In animal reproduction studies, oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryo lethality at systemic exposure (AUC) similar to the recommended clinical dose. A similar effect was not seen in rats even at very high systemic exposure.

Abacavir demonstrated toxicity to the developing embryo and foetus in rats, but not in rabbits. These findings included decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and still births. No conclusion can be drawn about the teratogenic potential of abacavir because of this embryo-foetal 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 Microcrystalline cellulose
Sodium starch glycolate
Sucralose
Crospovidone
Magnesium stearate
Strawberry flavour

6.2 Incompatibilities Not applicable.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container
White, opaque, HDPE bottle with a canister of 3g silica gel and purified cotton and closed with a white, round, polypropylene child resistant cap with a head induction foil inner seal. Pack sizes: 30s and 60s tablets.

6.6 Special precautions for disposal and other handling No special precautions.

7. APPLICANT

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