WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*] https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA494 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 351.3 mg abacavir sulfate equivalent to 300 mg abacavir.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Abacavir (as sulfate) 300 mg tablets are dark yellow coloured, film-coated, biconvex, capsule shaped tablets, with "AB" embossed on one side and a break-line on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA494 trade name] is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children. See also section 4.4 concerning [HA494 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).

[HA494 trade name] may be used as part of a regimen for post-exposure prophylaxis to HIV. For use of antiretroviral agents for post-exposure prophylaxis 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

Adults, adolescents and children weighing at least 25 kg:

The recommended dose of [HA494 trade name] is 600 mg daily. This may be administered as either 300 mg (one tablet) twice daily or 600 mg (two tablets) once daily (see sections 4.4 and 5.1).

Children under 25 kg:

Twice daily dosing

Weight	Morning Dose	Evening dose
20 kg - 24.9 kg	½ tablet (150 mg)	1 tablet (300 mg)
14 kg – 19.9 kg	½ tablet (150 mg)	½ tablet (150 mg)

Once daily dosing

Weight	Daily dose
20 kg - 24.9 kg	1 ½ tablets (450 mg)
14 kg – 19.9 kg	1 tablet (300 mg)

Special Populations

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

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.

Renal impairment:

[HA494 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 [HA494 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

[HA494 trade name] can be taken with or without food.

4.3 Contraindications

Hypersensitivity to abacavir 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

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.
- [HA494 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.
- [HA494 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 [HA494 trade name] after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with [HA494 trade name] for reasons of a suspected HSR, [HA494 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 [HA494 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 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 [HA494 trade name] might be higher than with other therapeutic options (see section 5.1).

Liver disease

The safety and efficacy of [HA494 trade name] has not been established in patients with significant underlying liver disorders. [HA494 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.

Renal disease

[HA494 trade name] should not be administered to patients with end-stage renal disease (see section 5.2)

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 autoimWERTYmune 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 aetiology 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 abacavir 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.

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 [HA494 trade name], action should be taken to minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia).

4.5 Interaction with other medicinal products and other forms of interaction

[HA494 trade name] contains abacavir.

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.

Abacavir is not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) nor does it inhibit or induce this enzyme system. Abacavir shows limited potential to inhibit metabolism mediated by CYP3A4 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 medicinal products metabolised by major P450 enzymes.

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.
Zidovudine/Abacavir	Interaction not studied	
ANTI-INFECTIVE PRODUCTS		
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Abacavir	Interaction not studied.	No [HA494 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
Flucloxacillin/Abacavir	Potential hepatotoxicity.	HLA-5701 genotyping is recommended.
ANTIMYCOBACTERIALS		
Rifampicin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
ANTICONVULSANTS		
Carbamazepine/Abacavir	Potential interaction likely to be of weak intensity.	Dosage adjustment is unlikely to be required
Phenobarbital/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Phenytoin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment. Monitor phenytoin concentrations.
ANTIHISTAMINES (HISTAMINE H2 RECEPTOR ANTAGONISTS)		
Ranitidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.

Drugs by Therapeutic Area	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration
Cimetidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
CYTOTOXICS		
Fluorouracil/Abacavir	Potential interaction likely to be of weak intensity.	Additional action/monitoring or dosage adjustment is unlikely to be required
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 [HA494 trade name] dosage adjustment necessary. Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration may be required.
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.
MISCELLANEOUS		
Clopidogrel/Abacavir	Pharmacodynamic effect of clopidogrel may be reduced.	An alternative NRTI or antiplatelet agent should be considered.
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.
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.
Orlistat/Abacavir	Potential interaction likely to be of weak intensity.	Additional action/monitoring or dosage adjustment is unlikely to be required

Drugs by Therapeutic Area	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning 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)

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

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

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

[HA494 trade name]can be used in pregnancy if clinically needed.

[HA494 trade name]should not be initiated during pregnancy, due to the risk of a hypersensitivity reaction to abacavir. If a patient becomes pregnant during treatment with[HA494 trade name], 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).

Breastfeeding

Abacavir is excreted into 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

There are no data on the effects of [HA494 trade name] on human male or female fertility Studies in animals showed that abacavir had no effect on fertility (see also section 5.3).

4.7 Effects on ability to drive and use machines

No studies are available on the effects of [HA494 trade name] on the ability to drive and use machines. Nevertheless, the clinical status of the patient and the adverse reaction profile of [HA494 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 [HA494 trade name] are consistent with the known safety profile of abacavir. 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 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**
Immune system disorders	Common: hypersensitivity
Metabolism and nutrition disorders	Common: anorexia Very rare: lactic acidosis
Nervous system disorders	Common: headache
Gastrointestinal disorders	Common: nausea, vomiting, diarrhoea Rare: pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain
Skin and subcutaneous tissue disorders	Common: rash (without systemic symptoms) Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
General disorders and administration site conditions	Common: fever, lethargy, fatigue.

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
Renal	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

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 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. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nucleoside reverse transcriptase inhibitors,

ATC Code: J05AF06

Mechanism of action

Abacavir is an NRTI. Abacavir is metabolised intracellularly to the active moiety, carbovir 5'- triphosphate (TP). In vitro studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event which results in chain termination and interruption of the viral replication cycle.

The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Clinical efficacy

Adults

The demonstration of the benefit of abacavir is mainly based on results of studies performed in adult treatment-naïve patients using a regimen of Ziagen 300 mg twice daily in combination with zidovudine and lamivudine. 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 vitro resistance

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro*, requiring multiple mutations for a clinically relevant increase in EC_{50} over wild-type virus.

In vivo resistance (Therapy naïve patients)

Isolates from most patients experiencing virological failure with a regimen containing abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline (45%) or only M184V or M184I selection (45%). The overall selection frequency for M184V or M184I was high (54%), and less common was the selection of L74V (5%), K65R (1%) and Y115F (1%). The inclusion of zidovudine in the regimen has been found to reduce the frequency of L74V and K65R selection in the presence of abacavir (with zidovudine: 0/40, without zidovudine: 15/192, 8%).

Phenotypic resistance and cross-resistance

Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple TAMs. Phenotypic cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir maintain their antiretroviral activities against such HIV-1 variants. The presence of M184V with K65R does give rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. The presence of M184V with Y115F gives rise to cross-resistance between abacavir and lamivudine. Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

Cross-resistance between abacavir and antiretrovirals from other classes (e.g., PIs or NNRTIs) is unlikely.

5.2 Pharmacokinetic properties

Absorption of [HA494 trade name]
The absorption characteristics of [HA494 trade name] have been determined after administration of a single dose tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation (geometric mean)**
Maximum concentration (C_{max})	3424 ± 1225 (3225) ng/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	7013 ± 2276 (6683) ng·h/mL
Time to attain maximum concentration (tmax)	0.6 ± 0.4h

Pharmacokinetics of Abacavir

General	NA*
Absorption	
Absolute bioavailability	83%
Oral bioavailability	At least 83%
Food effect	Concomitant food intake did not affect the extent of absorption but increased T_{max} and decreased C_{max}
Distribution	
Volume of distribution (mean)	0.8 L/kg
Plasma proteinbinding *in vitro*	Approximately 49% (binding to human plasma proteins)
Tissue distribution	CSF to plasma AUC ratio: 30 to 44%
Metabolism	
	hepatic metabolism followed by glucuronidation to produce 5'-carboxylic acid and 5'-glucuronide
Active metabolite(s)	None
Elimination	
Elimination half life	1.5 hours after single dose 21 hours for intracellular carbovir triphosphate
Mean systemic clearance (Cl/F)	NA*
% of dose excreted in urine	Approximately 2% excreted unchanged; total 83%
% of dose excreted in faeces	16%
Pharmacokinetic linearity	Linear pharmacokinetics and dose proportional over the range of 300-1200mg/day
Drug interactions (in vitro)	
Transporters	NA*
Metabolising Enzymes	Alcohol dehydrogenase, UDP-glucuronyltransferase

NA* = Information not available

Special populations

Hepatic impairment:
There are no data available on the use of abacavir in hepatically impaired patients.

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.

Renal impairment:

Pharmacokinetic data have been obtained for abacavir. 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.

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.

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.

Mutagenicity and carcinogenicity

Abacavir was not mutagenic in bacterial tests but showed activity *in vitro* in the human lymphocyte chromosome aberration assay, the mouse lymphoma assay, and the *in vivo* micronucleus test. These results indicate that abacavir has a weak potential to cause chromosomal damage, both *in vitro* and *in vivo*, at high concentrations.

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 was shown to cross the placenta.

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 with regard to the teratogenic potential of abacavir because of this embryo-foetal toxicity.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: colloidal silicon dioxide
magnesium stearate
microcrystalline cellulose
sodium starch glycolate.

Film coat: hypromellose
iron oxide yellow
macrogol 400
titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Blister pack

Plain Aluminium foil (width 126mm, thickness 0.020mm) and clear colourless or amber coloured PVC (width 130mm).

Pack size: 6x10 tablets in blister packs.

HDPE pack

- 75cc white opaque HDPE container [D:44.2xH:80.3mm] [38-400 Neck finish], with child resistant cap [outer-white opaque polypropylene, inner transparent polypropylene cap with induction sealing FS 5-4 liner]. –[38/400 Neck] [D:45xH17.80mm]
- 85cc round opaque HDPE container] lD:46.1xH:79.5mm] [38.5mm Neck finish], with 38mm HDPE white opaque closure with 7 layers induction sealing liner printed, “sealed for your protection”.

Pack size: 60 tablets in plastic containers.

6.6 Special precautions for disposal and other handling

No special requirements.

7. SUPPLIER

Strides Pharma Science Limited
Bilekahalli, Bannerghatta Road,
Bangalore -560076, India
Tel : 91-80-67840738/739
Fax: 91-80-67840200

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA494

9. DATE OF PREQUALIFICATION

22 December 2011

10. DATE OF REVISION OF THE TEXT

November 2022

References

General

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Section 4.6 and 5.3

Drug and Lactation Database (LactMed). Available at:
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REPROTOX® is a service of The Reproductive Toxicology Center, A Non-Profit Foundation located at:2737 Devonshire Pl NW #120 Washington DC 20008-3459 (2018). Available at:
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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines