SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Baclam 600mg/300mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Abacavir sulfate
Equivalent to Abacavir ..... 600 mg
Lamivudine ..... 300 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orange colored, capsule shaped, film-coated tablet, debossed with ' RF-90' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abacavir and Lamivudine (600/300 mg) tablets are indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, adolescents and children weighing at least 25 kg (see sections 4.4 and 5.1).

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

4.2 Posology and method of administration

Therapy should be prescribed by a physician experienced in the management of HIV infection.

Posology
Adults, adolescents and children weighing at least 25 kg:

The recommended dose of abacavir and lamivudine (600/300 mg) tablet is one tablet once daily.

Children Under 25 kg:
Abacavir and lamivudine (600/300 mg) tablets should not be administered to children who weigh less than 25 kg because it is a fixed-dose tablet that cannot be dose reduced.

Abacavir and lamivudine (600/300 mg) tablet is a fixed-dose tablet and should not be prescribed for patients requiring dose adjustments. Separate preparations of abacavir or lamivudine are available in cases where discontinuation or dose adjustment of one of the active substances is indicated. In these cases the physician should refer to the individual product information for these medicinal products.

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 the decrease in renal function and alteration of haematological parameters.

Renal impairment:
Abacavir and lamivudine (600/300 mg) tablet is not recommended for use in patients with a creatinine clearance < 50 ml/min as necessary dose adjustment cannot be made (see section 5.2).

Hepatic impairment:
Abacavir is primarily metabolised by the liver. No clinical data are available in patients with moderate or severe hepatic impairment, therefore the use of abacavir and lamivudine (600/300 mg) tablet is not recommended unless judged necessary. In patients with mild hepatic impairment (Child-Pugh score 5-6) close monitoring is required, including monitoring of abacavir plasma levels if feasible (see sections 4.4 and 5.2).

Paediatric population:
The safety and efficacy of abacavir and lamivudine (600/300 mg) tablet in children weighing less than 25 kg has not been established.

Currently reported data are described in section 4.8, 5.1 and 5.2 but no recommendation on posology can be made.

Method of administration

Oral use
Abacavir and lamivudine (600/300 mg) tablet can be taken with or without food.

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 abacacir and lamivudine tablet.

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

Hypersensitivity reactions (see also section 4.8)
Abacavir is associated with a risk for hypersensitivity reactions (HSR) [see section 4.8] characterised 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.
- Abacavir and lamivudine tablets 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 *[e. g. Fixed dose combination (FDC) of lamivudine, zidovudine and abacavir sulfate or FDC of lamivudine, abacavir sulfate, dolutegravir sodium].*
- **Abacavir and lamivudine tablets 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 abacavir and lamivudine tablets after the onset of hypersensitivity may result in a life-threatening reaction.

After stopping treatment with abacavir and lamivudine tablets for reasons of a suspected HSR, abacavir and lamivudine tablets or **any other medicinal product containing abacavir (e. g. FDC of lamivudine, zidovudine and** abacavir sulfate or FDC of lamivudine, abacavir sulfate, dolutegravir sodium) 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 abacavir and lamivudine tablets

Clinical Description of abacavir HSR
Abacavir HSR has been well characterised. 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 and/or rash. Other signs and symptoms that have been reported 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.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines.

Lipid disorders should be managed as clinically appropriate.

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

Risk of virological failure
- ***Triple nucleoside therapy***: There have been reports of a high rate of virological failure, and of emergence of resistance 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 abacavir and lamivudine tablets might be higher than with other therapeutic options (see section 5.1).

Liver disease
The safety and efficacy of abacavir and lamivudine tablet has not been established in patients with significant underlying liver disorders. Abacavir and lamivudine tablet is not recommended in patients with moderate or severe hepatic impairment (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction, including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

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 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 lamivudine is being used concomitantly for the treatment of HIV and hepatitis B virus (HBV), additional information relating to the use of lamivudine in the treatment of hepatitis B infection can be found in the Summary of Product Characteristics for products containing lamivudine that are indicated for the treatment of HBV.

If abacavir and lamivudine tablet 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 (see the Summary of Product Characteristics for products containing lamivudine that are indicated for the treatment of HBV).

Mitochondrial dysfunction following exposure *in utero*
Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial

dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues: these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These reactions have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleotide and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

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

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients should be advised that abacavir and lamivudine tablet or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

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 reported clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from reported 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 abacavir and lamivudine tablet, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Drug Interactions:
Abacavir and lamivudine tablets should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

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

Excipients
Abacavir and lamivudine tablet contains the azo colouring agent sunset yellow, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Abacavir and lamivudine tablet contains abacavir and lamivudine, therefore any interactions identified for these individually are relevant to abacavir and lamivudine tablet. Reported 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 CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P450 enzymes.

Abacavir and lamivudine tablets 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, abacavir and lamivudine tablets should not be administered concomitantly with other cytidine analogues, such as emtricitabine.
ANTI-INFECTIVE PRODUCTS		
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Abacavir	Interaction not studied.	No dosage adjustment necessary for abacavir and lamivudine tablet.
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)	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.
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	Insufficient data to recommend dosage adjustment.

	concentrations through UGT induction.	
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 dosage adjustment necessary for abacavir and lamivudine tablet. Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration
Methadone/Lamivudine	Interaction not studied.	
		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.
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.	

Abbreviations: ↑ = Increase; ↓ = decrease; ↔ = no significant change; AUC = area under the concentration versus time curve; Cmax = maximum observed concentration; CL/F = apparent oral clearance

Paediatric population
Interaction studies have only been performed in adult.

4.6 Fertility, pregnancy and lactation

Pregnancy
As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account.

Animal studies with abacavir have shown toxicity to the developing embryo and foetus in rats, but not in rabbits. Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats (see section 5.3). The active ingredients of abacavir and lamivudine tablet may inhibit cellular DNA replication and abacavir has been shown to be carcinogenic in animal models (see section 5.3). The clinical relevance of these findings is unknown. Placental transfer of abacavir and lamivudine has been shown to occur in humans.

In pregnant women treated with abacavir, more than 800 outcomes after first trimester exposure and more than 1000 outcomes after second and third trimester exposure indicate no malformative and foetal/neonatal effect. In pregnant women treated with lamivudine, more than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure indicate no malformative and foeto/neonatal effect. There are no data on the use of abacavir and lamivudine tablet in pregnancy, however the malformative risk is unlikely in humans based on those data.

For patients co-infected with hepatitis who are being treated with a lamivudine containing medicinal product such as abacavir and lamivudine tablet and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

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 its metabolites are excreted into the milk of lactating rats. Abacavir is also excreted into human milk.

Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of abacavir and lamivudine when administered to babies less than three months old.

It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

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 on the effects on ability to drive and use machines have been performed. The clinical status of the patient and the adverse reaction profile of abacavir and lamivudine tablets 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 abacavir and lamivudine tablet 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).

Body system	**Abacavir**	**Lamivudine**
Blood and lymphatic systems disorders		Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia 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) Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Common: Rash, alopecia Rare: Angioedema
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. 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 instance, 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) 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 CART. The frequency of this is unknown (see section 4.4).

Paediatric population
The safety to support once daily dosing in paediatric patients is based on reported study in which 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 abacavir and lamivudine tablet 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. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority via Pharmacovigilance Electronic

Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

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

Mechanism of action: Abacavir and lamivudine are NRTIs, and are potent selective inhibitors of HIV-1 and HIV-2 (LAV2 and EHO) replication. Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective 5'-triphosphate (TP) which are the active moieties. Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates 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.

Resistance

In vivo resistance

Abacavir-resistant isolates of HIV-1 have been selected *in-vitro* in wild-type strain HIV-1 (HXB2) and are associated with specific genotypic changes in the RT codon region (codons M184V, K65R, L74V and Y115). Selection for the M184V mutation occurred first and resulted in a two fold increase in IC50. Continued passage in increasing concentrations of drug resulted in selection for double RT mutants 65R/184V and 74V/184V or triple RT mutant 74V/115Y/184V. Two mutations conferred a 7- to 8-fold change in abacavir susceptibility and combinations of three mutations

were required to confer more than an 8-fold change in susceptibility. Passage with a zidovudine resistant clinical isolate RTMC also selected for the 184V mutation.

HIV-1 resistance to lamivudine involves the development of a M184I or, more commonly, M184V amino acid change close to the active site of the viral RT. Passage of HIV-1 (HXB2) in the presence of increasing 3TC concentrations results in high-level (>100 to >500-fold) lamivudine-resistant viruses and the RT M184I or V mutation is rapidly selected. The IC_{50} for wild-type HXB2 is 0.24 to
0.6 μM, while the IC_{50} for M184V containing HXB2 is >100 to 500 μM.

Antiviral therapy According to Genotypic/Phenotypic Resistance

In vivo resistance (Therapy-naïve patients)
The M184V or M184I variants arise in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy.

Isolates from most patients experiencing virological failure with a regimen containing abacavir in reported 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%) (see table below). 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%).

Therapy	**Abacavir + FDC of lamivudine and zidovudine**	**Abacavir + lamivudine + NNRTI**	**Abacavir + lamivudine + PI (or PI/ritonavir)**	**Total**
Number of Virological Failures	43	90	158	306
Number of On-Therapy Genotypes	40 (100%)	51 (100%)*	141 (100%)	232 (100%)
K65R	0	1 (2%)	2 (1%)	3 (1%)
L74V	0	9 (18%)	3 (2%)	12 (5%)
Y115F	0	2 (4%)	0	2 (1%)
M184V/I	34 (85%)	22 (43%)	70 (50%)	126 (54%)
TAMs$	3 (8%)	2 (4%)	4 (3%)	9 (4%)

* Includes three non-virological failures and four unconfirmed virological failures.
$ Number of subjects with ≥1 Thymidine Analogue Mutations (TAMs).

TAMs might be selected when thymidine analogs are associated with abacavir. In a reported meta-analysis of six clinical trials, TAMs were not

selected by regimens containing abacavir without zidovudine (0/127), but were selected by regimens containing abacavir and the thymidine analogue zidovudine (22/86, 26%).

In vivo resistance (Therapy experienced patients)
The M184V or M184I variants arise in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy and confer high-level resistance to lamivudine. Reported *in vitro* data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTIs should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTIs are available.

Clinically significant reduction of susceptibility to abacavir has been reported in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. In a reported meta-analysis of five clinical trials where ABC was added to intensify therapy, 74% of patients had M184V/I, 30% had T215Y/F, 27% had M41L, 18% had K70R and 15% had D67N. K65R was absent and L74V and Y115F were uncommon (≤3%). Logistic regression modelling of the predictive value for genotype (adjusted for baseline plasma HIV-1RNA [vRNA], CD4+ cell count, number and duration of prior antiretroviral therapies) showed that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at Week 4 (p=0.015) or 4 or more mutations at median Week 24 (p≤0.012). In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, cause a high level of resistance to abacavir.

Baseline Reverse Transcriptase Mutation	**Week 4**	
	Median Change vRNA (log10 c/mL)	**Percent with <400 copies/mL vRNA**
None	-0.96	40%
M184V alone	-0.74	64%
Any one NRTI mutation	-0.72	65%
Any two NRTI-associated mutations	-0.82	32%
Any three NRTI-associated mutations	-0.30	5%
Four or more NRTI-associated mutations	-0.07	11%

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. Readily available genotypic drug resistance interpretation algorithms and commercially available susceptibility tests have established clinical cut offs for reduced activity for abacavir and lamivudine as separate drug entities that predict susceptibility, partial susceptibility or resistance based upon either direct measurement of susceptibility or by calculation of the HIV-1 resistance phenotype from the viral genotype. Appropriate use of abacavir and lamivudine can be guided using these currently 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

The fixed-dose combination tablet of abacavir/lamivudine (FDC) has been shown to be bioequivalent to lamivudine and abacavir administered separately.

It has been reported that there is no clinically significant food effect observed between administration of FDC in the fasted or fed state and therefore, FDC can be taken with or without food.

The pharmacokinetic properties of lamivudine and abacavir are described below.

Absorption
Abacavir and lamivudine are rapidly and well absorbed from the gastro-intestinal tract following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is about 83% and 80-85% respectively. The mean time to maximal serum concentrations (t_{max}) is about 1.5 hours and 1.0 hour for abacavir and lamivudine, respectively. Following a single dose of 600 mg of abacavir, the mean (CV) C_{max} is 4.26 µg/ml (28%) and the mean (CV) AUC_{∞} is
11.95 µg.h/ml (21%). Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days, the mean (CV) steady-state C_{max} is 2.04 µg/ml (26%) and the mean (CV) AUC24 is 8.87 µg.h/ml (21%).

Distribution
The mean apparent volume of distribution for abacavir and lamivudine is 0.8 and 1.3 l/kg, respectively. Abacavir binds only low to moderately (~49%) to

human plasma proteins at therapeutic concentrations. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited plasma protein binding *in vitro* (< 36%). This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement.

Abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). A CSF to plasma AUC ratio of between 30 to 44% has been reported for abacavir. The observed values of the peak concentrations are 9 fold greater than the IC_{50} of abacavir of 0.08 μg/ml or 0.26 μM when abacavir is given at 600 mg twice daily. The mean ratio of CSF/serum lamivudine concentrations 2-4 hours after oral administration was approximately 12%. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

Biotransformation
Abacavir is primarily metabolised by the liver with approximately 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. These metabolites are excreted in the urine.

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of unchanged lamivudine. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5-10%).

Elimination
The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant accumulation of abacavir. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine. The remainder is eliminated in the faeces.

The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, predominantly by renal clearance (> 70%) via the organic cationic transport system. Reported studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Abacavir and lamivudine tablet is not recommended for use in patients with a creatinine clearance < 50 ml/min as necessary dose adjustment cannot be made (see section 4.2).

Intracellular pharmacokinetics
In a reported study of HIV-infected patients receiving abacavir 300 mg twice daily, with only one 300 mg dose taken prior to the 24 hour sampling period, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was
20.6 hours, compared to the geometric mean abacavir plasma half-life in this study of 2.6 hours. In a reported crossover study in HIV-infected patients, intracellular carbovir-TP exposures were higher for the abacavir 600 mg once daily regimen ($AUC_{24,ss}$ + 32%, $C_{max24,ss}$ + 99% and

Ctrough + 18%) compared to the 300 mg twice daily regimen. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16-19 hours, compared to the plasma lamivudine half-life of 5-7 hours. In another crossover study in healthy volunteers, intracellular lamivudine-TP pharmacokinetic parameters were similar ($AUC_{24,ss}$ and $C_{max24,ss}$) or lower (C_{trough} –24%) for the lamivudine 300 mg once daily regimen compared to the lamivudine 150 mg twice daily regimen. Overall, these reported data support the use of lamivudine 300 mg and abacavir 600 mg once daily for the treatment of HIV-infected patients. Additionally, the efficacy and safety of this combination given once daily has been demonstrated in a reported pivotal clinical study.

Special patient populations

Hepatic impairment
Pharmacokinetic data has been obtained for abacavir and lamivudine separately.

Abacavir is metabolised primarily by the liver. A mean increase of 1.89 fold in the abacavir AUC, and 1.58 fold in the elimination half-life has been reported in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. No definitive recommendation on dose reduction is possible in patients with mild hepatic impairment due to substantial variability of abacavir exposure.

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

Based on reported data obtained for abacavir, abacavir and lamivudine tablet 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 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.

Increase in plasma concentrations (AUC) of lamivudine has been reported in patients with renal dysfunction due to decreased clearance. Abacavir and lamivudine tablet is not recommended for use in patients with a creatinine clearance < 50 ml/min as necessary dose adjustment cannot be made.

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

Children

Abacavir is rapidly and well absorbed from oral formulations when administered to children. It has been reported that in paediatric, once daily dosing provides equivalent AUC24 to twice daily dosing of the same total daily dose for both oral solution and tablet formulations.

5.3 Preclinical safety data

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

Mutagenicity and carcinogenicity
Neither abacavir nor lamivudine were mutagenic in bacterial tests, but consistent with other nucleoside analogues, they inhibit cellular DNA replication in reported *in vitro* mammalian tests such as the mouse lymphoma assay. The results of an reported *in vivo* rat micronucleus test with abacavir and lamivudine in combination were negative.

Lamivudine has not shown any genotoxic activity in the reported *in vivo* studies at doses that gave plasma concentrations up to 40-50 times higher than clinical plasma concentrations. 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. In reported long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. Reported 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.

The majority 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.

Repeat-dose toxicity
In reported 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 reported 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 reported 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.

Reproductive toxicology

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

Lamivudine was not teratogenic in animal studies but there were indications of an increase in early embryonic deaths in rabbits at relatively low systemic exposures, comparable to those achieved in humans. A similar effect was not seen in rats even at very high systemic exposure.

Toxicity to the developing embryo and foetus in rats, but not in rabbits has been reported with Abacavir. 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 reported 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, colloidal silicon dioxide, magnesium stearate, sodium starch glycolate, Opadry Orange YS-1-13065-A (Polysorbate 80, Hypromellose 3mPas, Hypromellose 6mPas, Titanium dioxide, Macrogol, FD&C yellow #6/Sunset Yellow FCF Aluminum Lake).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Keep out of reach and sight of children.

Store below 30°C. Avoid excursions above 30°C.

Do not use after the expiry date. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines no longer use. These measures will help protect the environment.

6.5 Nature and contents of container

'30's and 90's HDPE Bottle pack comprising of white opaque HDPE bottle having a polypropylene child resistant closure or screw closure.

30's and 90's Bottle Pack; the bottle to be supplied with or without a carton

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING ADRESS

Sun Pharmaceutical Industries Limited
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Goregaon(East),
Mumbai-400063, *Maharashtra, India*

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