Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Abacavir/Lamivudine 600 mg/300 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of abacavir and 300 mg of lamivudine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Orange, oblong, biconvex film-coated tablets with debossing 600 on one side and 300 on the other side with dimension of ~ 20.5 mm x 9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Abacavir/Lamivudine is 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/Lamivudine is one tablet once daily.

Children Under 25 kg:
Abacavir/Lamivudine 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/Lamivudine 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/Lamivudine 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:
Abacaviris primarily metabolised by the liver. No clinical data are available in patients with moderate or severe hepatic impairment, therefore the use of Abacavir/Lamivudine is not recommended unless judged necessary. In patients with mild hepatic impairment (Child-Pugh score5-6) 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/Lamivudine in children weighing less than 25 kg has not been established.

Currently available 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/Lamivudine 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 the combination of abacavir and lamivudine.

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/Lamivudine 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.
• The combination of abacavir and lamivudine **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 the combination of abacavir and lamivudine after the onset of hypersensitivity may result in a life-threatening reaction.
• After stopping treatment with the combination of abacavir and lamivudine for reasons of a suspected HSR, Abacavir/Lamivudine **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 Abacavir/Lamivudine tablets

Clinical Description of abacavir HSR

Abacavir HSR has been well characterised 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 and/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), orgastroenteritis.**

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 the combination of abacavir and lamivudine might be higher than with other therapeutic options (see section 5.1).

Liver disease
The safety and efficacy of the combination of abacavir and lamivudine has not been established in patients with significant underlying liver disorders. The combination of abacavir and lamivudine is not recommended in patients with moderate or severe hepatic impairment (see section 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 the combination of abacavir and lamivudine 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 *inutero* 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 nucleoside and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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 *Pneumocystiscarinii* pneumonia. 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 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 the combination of abacavir and lamivudine 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 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 the combination of abacavir and lamivudine, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Drug Interactions
The combination of abacavir and lamivudine 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).

4.5 Interaction with other medicinal products and other forms of interactions

This medicinal product contains abacavir and lamivudine, therefore any interactions identified for these individually are relevant to this medicinal product. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine.

Abacavir is metabolised by UDP-glucuronyl transferase (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/Lamivudine 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/Lamivudine 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 for Abacavir/Lamivudine 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	Insufficient data to recommend dosage adjustment.

	through UGT induction.	
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.	Therefore, the concomitant use of

	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	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 for Abacavir/Lamivudine 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/600mg 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	When possible, avoid chronic coadministration of

	Lamivudine: AUC ↓14%; 32%; 36% Cmax ↓28%; 52%, 55%.	Abacavir/lamivudine 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.

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

Paediatric population
Interaction studies have only been performed in adults.

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 the combination of abacavir and lamivudine 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 the combination of abacavir and lamivudine 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 the combination of abacavir and lamivudine 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 mo thers 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 the combination of abacavir and lamivudine 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 the combination of abacavir and lamivudine 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*: lacticacidosis	*Very rare*: lacticacidosis
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	*Common:* Nausea, vomiting, abdominal pain or cramps, diarrhoea *Rare:* Rises in serum amylase. Cases of pancreatitis have been reported

	reported, but a causal relationship to abacavir treatment is uncertain	
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-Johns on 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. 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 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 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 CART. 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 fixed dose combination tablets 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6767836; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 systemic use, antivirals for treatment of HIV infections, combinations. ATC code: J05AR02.

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 abacavirin cell culture was not antagonized when combined with the nucleo side reverse

transcriptase inhibitors (NRTIs)didanosine, emtricitabine, stavudine, tenofovirorzidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Antiviral Activity *in vitro*

Both abacavir and lamivudine have been shown to inhibit replication of laboratory strains and clinical isolates of HIV in a number of cell types, including transformed T cell lines, monocyte/macrophage derived lines and primary cultures of activated peripheral blood lymphocytes (PBLs) and monocyte/macrophages. The concentration of drug necessary to effect viral replication by 50% (EC^{50}) or 50% inhibitory concentration (IC^{50}) varied according to virus and host cell type.

The mean $EC_{50}$for abacavir against laboratory strains of HIV-1IIIB and HIV-1HXB2 ranged from 1.4 to 5.8 µM. The median or mean EC_{50}values for lamivudine against laboratory strains of HIV-1 ranged from 0.007 to 2.3 µM. The mean EC_{50}against laboratory strains of HIV-2 (LAV2 and EHO) ranged from 1.57 to 7.5 µM for abacavir and from 0.16 to 0.51 µM for lamivudine.

The EC_{50}values of abacavir against HIV-1 Group M subtypes (A-G) ranged from 0.002 to 1.179 µM, against Group O from 0.022 to 1.21 µM, and against HIV-2 isolates, from 0.024 to 0.49 µM. For lamivudine, the EC_{50}values against HIV-1 subtypes (A-G) ranged from 0.001 to 0.170 µM, against Group O from 0.030 to 0.160 µM and against HIV-2 isolates from 0.002 to 0.120 µM in peripheral blood mononuclear cells.

Baseline HIV-1 samples from therapy-naive subjects with no amino acid substitutions associated with resistance have been evaluated using either the multi-cycle Virco Antivirogram™ assay (n=92 from COL40263) or thesingle cycle Monogram Biosciences PhenoSense™ assay (n=138 from ESS30009). These resulted in median EC_{50}values of 0.912 µM (range: 0.493 to 5.017 µM) and 1.26 µM (range 0.72 to 1.91 µM) respectively for abacavir, and median EC_{50}values of 0.429 µM (range: 0.200 to 2.007 µM) and 2.38 µM (1.37 to 3.68 µM) respectively for lamivudine.

Phenotypic susceptibility analyses of clinical isolates from antiretroviral-naïve patients with HIV-1 Group M non-B subtypes in three studies have each reported that all viruses were fully susceptible to both abacavir and lamivudine; one study of 104 isolates that included subtypes A and A1 (n=26), C (n=1), D (n=66), and the circulating recombinant forms (CRFs) AD (n=9), CD (n=1), and a complex inter-subtype recombinant_cpx (n=1), a second study of 18 isolates including subtype G (n=14) and CRF_AG (n=4) from Nigeria, and a third study of six isolates (n=4 CRF_AG, n=1 A and n=1 undetermined) from Abidjan (Côte d'Ivoire).

HIV-1 isolates (CRF01_AE, n=12; CRF02_AG, n=12; and Subtype C or CRF_AC, n=13) from 37 untreated patients in Africa and Asia were susceptible to abacavir (IC_{50}fold changes < 2.5), and lamivudine (IC_{50}fold changes < 3.0), except for two CRF02_AG isolates with fold-changes of 2.9 and 3.4 for abacavir. Group O isolates from antiviral naïve patients tested for lamivudine activity were highly sensitive.

The combination of abacavir and lamivudine has demonstrated antiviral activity in cell culture against non-subtype B isolates and HIV-2 isolates with equivalent antiviral activity as for subtype B isolates.

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 IC^{50}. 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 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 + Combivir[1]**	**Abacavir + lamivudine + NNRTI**	**Abacavir + lamivudine + PI (or PI/ritonavir)**	**Total**
Number of Subjects	282	1094	909	2285
Number of Virological Failures	43	90	158	306
Number of On-Therapy Genotypes	40 (100%)	51 (100%)[2]	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]	3 (8%)	2 (4%)	4 (3%)	9 (4%)

1. Combivir is a fixed dose combination of lamivudine and zidovudine
2. Includes three non-virological failures and four unconfirmed virological failures.
3. Number of subjects with ≥1 Thymidine Analogue Mutations (TAMs).

TAMs might be selected when thymidine analogs are associated with abacavir. In a 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 anti-retroviral therapy and confer high-level resistance to lamivudine. *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 demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. In a meta-analysis of five clinical trials where ABC was added to intensify therapy, of 166 subjects, 123 (74%) had M184V/I, 50 (30%) had T215Y/F, 45 (27%) had M41L, 30 (18%) had K70R and 25 (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 ($p\leq0.012$). 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 (n = 166)**		
	n	**Median Change vRNA (log_{10} c/mL)**	**Percent with <400 copies/mL vRNA**
None	15	-0.96	40%
M184V alone	75	-0.74	64%
Any one NRTI mutation	82	-0.72	65%
Any two NRTI associated mutations	22	-0.82	32%
Any three NRTI associated mutations	19	-0.30	5%

Four or more NRTI associated mutations	28	-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.

Clinical experience

Clinical experience with the combination of abacavir and lamivudine as a once daily regimen is mainly based on four studies in treatment-naïve subjects, CNA30021, EPZ104057 (HEAT study), ACTG5202, and CNA109586 (ASSERT study) and two studies in treatment-experienced subjects, CAL30001 and ESS30008.

Therapy-naïve patients

The combination of abacavir and lamivudine as a once daily regimen is supported by a 48 weeks multi-centre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. These were primarily asymptomatic HIV infected patients (CDC stage A). They were randomised to receive either abacavir (ABC) 600 mg once daily or 300 mg twice daily, in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. The results are summarised by subgroup in the table below:

Efficacy Outcome at Week 48 in CNA30021 by baseline HIV-1 RNA and CD4 Categories (ITTe TLOVR ART naïve subjects)

	ABC QD +3TC+EFV (n=384)	**ABC BID +3TC+EFV (n=386)**
ITT-E Population TLOVR analysis	Proportion with HIV-1 RNA <50 copies/ml	
All Subjects	253/384 (66%)	261/386 (68%)
Baseline RNA category <100,000 copies/mL	141/217 (65%)	145/217 (67%)
Baseline RNA category >=100,000 copies/mL	112/167 (67%)	116/169 (69%)
Baseline CD4 category <50	3/6 (50%)	4/6 (67%)
Baseline CD4 category 50-100	21/40 (53%)	23/37 (62%)
Baseline CD4 category 101-200	57/85 (67%)	43/67 (64%)
Baseline CD4 category 201-350	101/143 (71%)	114/170 (67%)
Baseline CD4 category >350	71/109 (65%)	76/105 (72%)
>1 log reduction in HIV RNA or <50 cp/mL All Patients	372/384 (97%)	373/386 (97%)

Similar clinical success (point estimate for treatment difference: -1.7, 95% CI –8.4, 4.9) was observed for both regimens. From these results, it can be concluded with 95% confidence that the true difference is no greater than 8.4% in favour of the twice daily regimen. This potential difference is sufficiently small to draw an overall conclusion of non-inferiority of abacavir once daily over abacavir twice daily.

There was a low, similar overall incidence of virologic failure (viral load > 50 copies/ml) in both the once and twice daily treatment groups (10% and 8% respectively). In the small sample size for genotypic analysis, there was a trend toward a higher

rate of NRTI-associated mutations in the once daily versus the twice daily abacavir regimens. No firm conclusion could be drawn due to the limited data derived from this study.

There are conflicting data in some comparative studies with the combination of abacavir and lamivudine i.e. HEAT, ACTG5202 and ASSERT:

EPZ104057 (HEAT study) was a randomised, double-blind, placebo-matched, 96 week, multi-centre study with the primary objective of evaluating the relative efficacy of abacavir/lamivudine (ABC/3TC, 600mg/300mg) and tenofovir /emtricitabine (TDF/FTC, 300mg/200mg), each given once-daily in combination with lopinavir/ritonavir (LPV/r, 800mg/200mg) in HIV-infected, therapy-naive adults. The primary efficacy analysis was performed at week 48 with study continuation to week 96 and demonstrated non-inferiority. The results are summarised below:

Virologic Response Based on Plasma HIV-1 RNA < 50 copies/ml
ITT-Exposed Population M=F switch included

Virologic Response	**ABC/3TC +LPV/r (N = 343)**		**TDF/FTC + LPV/r (N = 345)**	
	Week 48	**Week 96**	**Week 48**	**Week 96**
Overall response (stratified by baseline HIV-1 RNA)	231/343 (68%)	205/343 (60%)	232/345 (67%)	200/345 (58%)
Response by Baseline HIV-1 RNA <100,000 c/ml	134/188 (71%)	118/188 (63%)	141/205 (69%)	119/205 (58%)
Response by Baseline HIV-1 RNA ≥100,000 c/ml	97/155 (63%)	87/155 (56%)	91/140 (65%)	81/140 (58%)

A similar virologic response was observed for both regimens (point estimate for treatment difference at week 48: 0.39%, 95% CI: -6.63, 7.40).

ACTG 5202 study was a, multi-centre, comparative, randomised study of double-blind abacavir/lamivudine or emtricitabine/tenofovir in combination with open-label efavirenz or atazanavir/ritonavir in treatment-naïve HIV-1 infected patients. Patients were stratified at screening based on plasma HIV-1 RNA levels < 100,000 and ≥ 100,000 copies/mL.

An interim analysis from ACTG 5202 revealed that abacavir/lamivudine was associated with a statistically significantly higher risk of virological failure as compared to emtricitabine/tenofovir (defined as viral load >1000 copies/mL at or after 16 weeks and before 24 weeks or HIV-RNA level >200 copies/mL at or after 24 weeks) in subjects with a screening viral load ≥100,000 copies/mL (estimated hazard ratio: 2.33, 95% CI: 1.46, 3.72, p=0.0003). The Data Safety Monitoring Board (DSMB) recommended that consideration be given to change in the therapeutic management of all subjects in the high viral load stratum due to the efficacy differences observed. The subjects in the low viral load stratum remained blinded and on-study.

Analysis of the data from subjects in the low viral load stratum showed no demonstrable difference between the nucleoside backbones in the proportion of patients free of virological failure at week 96. The results are presented below:

- 88.3% with ABC/3TC vs 90.3% with TDF/FTC when taken with atazanavir/ritonovir as third drug, treatment difference -2.0% (95% CI -7.5%, 3.4%),
- 87.4% with ABC/3TC vs 89.2% with TDF/FTC, when taken with efavirenz as third drug, treatment difference -1.8% (95% CI -7.5%, 3.9%).

CNA109586 (ASSERT study), a multi-centre, open label, randomised study of abacavir/lamivudine (ABC/3TC, 600mg/300mg) and tenofovir/emtricitabine (TDF/FTC, 300mg/200mg), each given once daily with efavirenz (EFV, 600mg) in ART naïve, HLA-B*5701 negative, HIV-1 infected adults. The virologic results are summarised in the table below:

Virologic Response at Week 48 ITT-Exposed Population < 50 copies/ml TLOVR

	ABC/3TC + EFV (N =192)	**TDF/FTC + EFV (N =193)**
Overall response	114/192 (59%)	137/193 (71%)
Response by Baseline HIV-1 RNA <100,000 c/mL	61/95 (64%)	62/83 (75%)

Response by Baseline HIV-1 RNA ≥100,000 c/mL	53/97 (55%)	75/110 (68%)

At week 48, a lower rate of virologic response was observed for ABC/3TC compared to TDF/FTC (point estimate for the treatment difference: 11.6%, 95% CI: 2.2, 21.1).

Therapy-experienced patients

Data from two studies, CAL30001 and ESS30008 demonstrated that the combination of abacavir and lamivudine once daily has similar virological efficacy to abacavir 300 mg twice daily plus lamivudine 300 mg once daily or 150 mg twice daily in therapy-experienced patients.

In study CAL30001, 182 treatment-experienced patients with virologic failure were randomised and received treatment with either the combination of abacavir and lamivudine once daily or abacavir 300 mg twice daily plus lamivudine 300 mg once daily, both in combination with tenofovir and a PI or an NNRTI for 48 weeks. Similar reductions in HIV-1 RNA as measured by average area under the curve minus baseline were observed, indicating that the combination of abacavir and lamivudine group was non-inferior to the abacavir plus lamivudine twice daily group (AAUCMB, -1.65 $\log_{10}$copies/ml versus -1.83 $\log_{10}$copies/ml respectively, 95% CI -0.13, 0.38). Proportions with HIV-1 RNA < 50 copies/ml (50% versus 47%) and < 400 copies/ml (54% versus 57%) at week 48 were also similar in each group (ITT population). However, as there were only moderately experienced patients included in this study with an imbalance in baseline viral load between the arms, these results should be interpreted with caution.

In study ESS30008, 260 patients with virologic suppression on a first line therapy regimen containing abacavir 300 mg plus lamivudine 150 mg, both given twice daily and a PI or NNRTI, were randomised to continue this regimen or switch to the combination of abacavir and lamivudine plus a PI or NNRTI for 48 weeks. Results at 48 weeks indicated that the combination of abacavir and lamivudine group was associated with a similar virologic outcome (non-inferior) compared to the abacavir plus lamivudine group, based on proportions of subjects with HIV-1 RNA < 50 copies/ml (90% and 85% respectively, 95% CI -2.7, 13.5).

A genotypic sensitivity score (GSS) has not been established by the MAH for the abacavir/lamivudine combination. The proportion of treatment-experienced patients in the CAL30001 study with HIV-RNA <50 copies/mL at Week 48 by genotypic sensitivity score in optimized background therapy (OBT) are tabulated The impact of major IAS-USA defined mutations to abacavir or lamivudine and multi-NRTI resistance associated mutations to the number of baseline mutations on response was also evaluated. The GSS was obtained from the Monogram reports with susceptible virus ascribed the values '1-4' based upon the numbers of drugs in the regimen and with virus with reduced susceptibility ascribed the value '0'. Genotypic sensitivity scores were not obtained for all patients at baseline. Similar proportions of patients in the once-daily and twice-daily abacavir arms of CAL30001 had GSS scores of <2 or ≥2 and successfully suppressed to <50 copies/mL by Week 48.

Proportion of Patients in CAL30001 with <50 copies/mL at Week 48 by Genotypic Sensitivity Score in OBT and Number of Baseline Mutations

	ABC/3TC FDC QD (n=94) Number of Baseline Mutations[1]				**ABC BID +3TC QD (n=88)**
Genotypic SS in OBT	All	0-1	2-5	6+	All
≤2	10/24 (42%)	3/24 (13%)	7/24 (29%)	0	12/26 (46%)
>2	29/56 (52%)	21/56 (38%)	8/56 (14%)	0	27/56 (48%)
Unknown	8/14 (57%)	6/14 (43%)	2/14 (14%)	0	2/6 (33%)
All	47/94 (50%)	30/94 (32%)	17/94 (18%)	0	41/88 (47%)

[1] Major IAS-USA defined mutations to Abacavir or Lamivudine and multi-NRIT resistance associated mutations
For the CNA109586 (ASSERT) and CNA30021 studies in treatment-naïve patients, genotype data was obtained for only a subset of patients at screening or at baseline, as well as for those patients who met virologic failure criteria. The partial patient subset of data available for CNA30021 is tabulated below, but must be interpreted with caution. Drug susceptibility scores were assigned for each patient's viral genotype utilising the ANRS 2009 HIV-1 genotypic drug resistance algorithm. Each susceptible drug in the regimen received a score of 1 and drugs for which the ANRS algorithm predicts resistance were ascribed the value '0'.

Proportion of Patients in CNA30021with <50 cps/mL at Week 48 by Genotypic Sensitivity Score in OBT and Number of Baseline Mutations

	ABC QD + 3TC QD + EFV QD (N=384) Number of Baseline Mutations[1]				**ABC BID+ 3TC QD + EFV QD (N=386)**
Genotypic SS in OBT	All	0-1	2-5	6+	All
≤2	2/6 (33%)	2/6 (33%)	0	0	3/6 (50%)
>2	58/119 (49%)	57/119 (48%)	1/119 (<1%)	0	57/114 (50%)
All	60/125 (48%)	59/125 (47%)	1/125 (<1%)	0	60/120 (50%)

[1] Major IAS-USA defined mutations to Abacavir or Lamivudine and multi-NRTI resistance associated mutations

Paediatric population

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. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight-band dosing recommendations in the World Health Organisation treatment guidelines(Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least an additional 96weeks. Within this population, 104 patients, weighing at least 25 kg, received 600 mg abacavir and 300 mg lamivudine as fixed dose combination tablets once daily, with a median duration of exposure of 596 days.

Among the 669 subjects randomized in this study (from12 months to ≤ 17years 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%, for the primary endpoint of<80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/mL, <400c/mL, <1000c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once versus twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

Among the 104 patients who received the combination of abacavir and lamivudine, including the ones who were between 40 kg and 25 kg, the viral suppression was similar.

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. This was demonstrated in a single dose, 3-way crossover bioequivalence study of FDC (fasted) versus 2 x 300 mg abacavir tablets plus 2 x 150 mg lamivudine tablets (fasted) versus FDC administered with a high fat meal, in healthy volunteers (n = 30). In the fasted state there was no significant difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration (C^{max}), of each component. There was also no clinically significant food effect observed between administration of FDC in the fasted or fed state. These results indicate that 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) $AUC_{24}$is 8.87 µg.h/ml (21%).

Distribution

Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0.8 and 1.3 l/kg respectively. Plasma protein binding studies *in vitro* indicate that 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.

Data show that abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44%. 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. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. The combination of abacavir and lamivudine 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 study of 20 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 crossover study in 27 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 C_{trough}+ 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 a crossover study in 60 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 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 pivotal clinical study (CNA30021- See Clinical experience).

Special patient populations

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

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 median (range)AUCvaluewas24.1(10.4to 54.8)ug.h/ml. The results showed that there was a mean (90%CI) increase of 1.89 fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No definitive recommendation on dose reduction is possible in patients with mild hepatic impairment due to 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.

Based on data obtained for abacavir, the combination of abacavir and lamivudine 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. Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. The fixed dose combination tablet of abacavir and lamivudine 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.

Paediatric population:
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.

5.3 Preclinical safety data

With the exception of a negative *in vivo* rat micronucleus test, there are no 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 *in vitro* mammalian tests such as the mouse lymphoma assay. The results of an *in vivo* rat micronucleus test with abacavir and lamivudine in combination were negative.

Lamivudine has not shown any genotoxic activity in the *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 long-term oral carcinogenicity studies in rats and mice, lamivudine 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.

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 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.

Reproductive toxicology

In 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.

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 and lamivudine had no effect on male or female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Hydroxypropyl cellulose
Sodium starch glycolate (type A)
Magnesium stearate

Film-coat:
Hypromellose
Macrogol 4000
Titanium dioxide (E171)
Polysorbate 80
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White PVC/PVDC//Al blisters.

Pack sizes of 10, 30 and 90 film-coated tablets in blisters or 10x1, 30x1 and 90x1 film-coated tablets in perforated unit-dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/242/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th October 2017

10 DATE OF REVISION OF THE TEXT

January 2020