SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect Sunset yellow FCF (E110) 1.46 mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Orange coloured, modified capsule shaped, film-coated tablets, debossed with ‘H’ on one side and ‘27’ on the other side. The size is 20.7 mm X 9.2 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 < 30 mL/min (see section 5.2). No dose adjustment is required in patients with mild or moderate renal impairment. However, the lamivudine exposure is significantly increased in patients with a creatinine clearance < 50 mL/min (see section 4.4).

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/lamivudine 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/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 abacavir/lamivudine.

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. (e.g. Ziagen, Trizivir, Triumeq)
- **Abacavir/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 Abacavir/Lamivudine after the onset of hypersensitivity may result in a life-threatening reaction.

- After stopping treatment with Abacavir/Lamivudine for reasons of a suspected HSR, Abacavir/Lamivudine **or any other medicinal product containing abacavir** (e.g.,Ziagen, Trizivir, Triumeq) **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), 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/lamivudine might be higher than with other therapeutic options (see section 5.1).

Liver disease

The safety and efficacy of abacavir/lamivudine has not been established in patients with significant underlying liver disorders. Abacavir/Lamivudine 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/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 *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 jirovecii* pneumonia (often referred to as PCP). Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and 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/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.

Cardiovascular events

Although the available data from clinical and observational studies with abacavir show inconsistent results, several studies suggest an increased risk of cardiovascular events (notably myocardial infarction) in patients treated with abacavir. Therefore, when prescribing abacavir/lamivudine, action should be

taken to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

In addition, alternative treatment options to the abacavir containing regimen should be considered when treating patients with a high cardiovascular risk.

Administration in subjects with moderate renal impairment

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

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

Drug Interactions

Abacavir/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).

Excipients

Abacavir/Lamivudine contains the azo colouring agent sunset yellow, which may cause allergic reactions.

Abacavir/Lamivudine contains Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Abacavir/Lamivudine contains abacavir and lamivudine, therefore any interactions identified for these individually are relevant to

abacavir/lamivudine. 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 induce this enzyme system. Lamivudine does not inhibit cytochrome P450 enzymes. Abacavir shows limited potential to inhibit metabolism mediated by CYP3A4 and has been shown *in vitro* not to inhibit CYP2C9 or CYP 2D6 enzymes. *In vitro* studies have shown that abacavir has potential to inhibit cytochrome P450 1A1 (CYP1A1). Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P450 enzymes.

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 abacavir/lamivudine dosage adjustment necessary. When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/ sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	
ANTIMYCOBACTERIALS		
Rifampicin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Rifampicin/Lamivudine	Interaction not studied.	
ANTICONVULSANTS		
Phenobarbital/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Phenobarbital/Lamivudine	Interaction not studied.	
Phenytoin/Abacavir	Interaction not studied.	Insufficient data to

	Potential to slightly decrease abacavir plasma concentrations through UGT induction.	recommend dosage adjustment.
Phenytoin/Lamivudine	Interaction not studied.	Monitor phenytoin concentrations.
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 abacavir/lamivudine dosage adjustment necessary. Methadone dosage adjustment unlikely in majority of patients; occasionally
Methadone/Lamivudine	Interaction not studied.	

		methadone re-titration may be required.
RETINOIDS		
Retinoid compounds (e.g. isotretinoin)/Abacavir	Interaction not studied. Possible interaction given common pathway of elimination via alcohol dehydrogenase.	Insufficient data to recommend dosage adjustment.
Retinoid compounds (e.g. isotretinoin)/Lamivudine No drug interaction studies	Interaction not studied.	
MISCELLANEOUS		
Ethanol/Abacavir (0.7 g/kg single dose/600 mg single dose)	Abacavir: AUC ↑41% Ethanol: AUC ↔ (Inhibition of alcohol dehydrogenase)	No dosage adjustment necessary.
Ethanol/Lamivudine	Interaction not studied.	
Sorbitol solution (3.2 g, 10.2 g, 13.4 g)/Lamivudine	Single dose lamivudine oral solution 300 mg Lamivudine: AUC ↓ 14%; 32%; 36% C_{max} ↓ 28%; 52%, 55%.	When possible, avoid chronic coadministration of 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.
Riociguat/Abacavir	Riociguat ↑ *In vitro*, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV	Riociguat dose may need to be reduced. Consult the riociguat prescribing

	patients receiving the combination of abacavir/dolutegravir/lamivudine (600mg/50mg/300mg once daily) led to an approximately three-fold higher riociguat $AUC_{(0-\infty)}$ when compared to historical riociguat $AUC_{(0-\infty)}$ reported in healthy subjects.	information for dosing recommendations.

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, both animal data as well as clinical experience in pregnant women should be taken into account.

Animal studies have shown toxicity to the developing embryo and foetus in rats, but not in rabbits (see section 5.3). Abacavir has been shown to be carcinogenic in animal models (see section 5.3). Clinical relevance in human of these data is unknown. Placental transfer of abacavir and/or its related metabolites has been shown to occur in human.

In pregnant women, 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 of abacavir. The malformative risk is unlikely in humans based on those data.

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. There are no data available on the safety of abacavir when administered to babies less than three months old. It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

Studies in animals showed that abacavir had no 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/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 abacavir/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		*Uncommon:* Neutropenia

systems disorders		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. 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 abacavir/lamivudine 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: nucleoside reverse transcriptase inhibitors,

ATC Code: J05AF06

Mechanism of action

Abacavir is a NRTI. It is a potent selective inhibitor of HIV-1 and HIV-2. Abacavir is metabolised intracellularly to the active moiety, carbovir 5'-triphosphate (TP). *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event which results in chain termination and interruption of the viral replication cycle. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Resistance

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

In vivo resistance (Therapy naïve patients)

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

	Abacavir +	**Abacavir +**	**Abacavir +**	

Therapy	Combivir[1]	lamivudine + NNRTI	lamivudine + PI (or PI/ritonavir)	Total
Number of Subjects	282	1094	909	2285
Number of Virological Failures	43	90	158	291
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)

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 abacavir 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-1 RNA [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. Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

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

Clinical efficacy and safety

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

Twice daily (300 mg) administration:

- *Therapy naïve adults*

In adults treated with abacavir in combination with lamivudine and zidovudine the proportion of patients with undetectable viral load (<400 copies/ml) was approximately 70% (intention to treat analysis at 48 weeks) with corresponding rise in CD4 cells.

One randomised, double blind, placebo controlled clinical study in adults has compared the combination of abacavir, lamivudine and zidovudine to the combination of indinavir, lamivudine and zidovudine. Due to the high proportion of premature discontinuation (42% of patients discontinued randomised treatment by week 48), no definitive conclusion can be drawn regarding the equivalence between the treatment regimens at week 48. Although a similar antiviral effect was observed between the abacavir and indinavir containing regimens in terms of proportion of patients with undetectable viral load (≤400 copies/ml; intention to treat analysis (ITT), 47% versus 49%; as treated analysis (AT), 86% versus 94% for abacavir and indinavir combinations respectively), results favoured the indinavir combination, particularly in the subset of patients with high viral load (>100,000 copies/ml at baseline; ITT, 46% versus 55%; AT, 84% versus 93% for abacavir and indinavir respectively).

In a multicentre, double-blind, controlled study (CNA30024), 654 HIV-infected, antiretroviral therapy-naïve patients were randomised to receive either abacavir 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily. The duration of double-blind treatment was at least 48 weeks. In the intent-to-treat (ITT) population, 70% of patients in the abacavir group, compared to 69% of patients in the zidovudine group, achieved a virologic response of plasma HIV-1 RNA ≤50 copies/ml by Week 48 (point estimate for treatment difference: 0.8, 95% CI -6.3, 7.9). In the as treated (AT) analysis the difference between both treatment arms was more noticeable (88% of patients in the abacavir group, compared to 95% of patients in the zidovudine group (point estimate for treatment difference: -6.8, 95% CI -11.8; 1.7). However, both analyses were compatible with a conclusion of non-inferiority between both treatment arms.

ACTG5095 was a randomised (1:1:1), double-blind, placebo-controlled trial performed in 1147 antiretroviral naïve HIV-1 infected adults, comparing 3 regimens: zidovudine (ZDV), lamivudine (3TC), abacavir (ABC), efavirenz (EFV) vs ZDV/3TC/EFV vs ZDV/3TC/ABC. After a median follow-up of 32

weeks, the tritherapy with the three nucleosides ZDV/3TC/ABC was shown to be virologically inferior to the two other arms regardless of baseline viral load (< or > 100 000 copies/ml) with 26% of subjects on the ZDV/3TC/ABC arm, 16% on the ZDV/3TC/EFV arm and 13% on the 4 drug arm categorised as having virological failure (HIV RNA >200 copies/ml). At week 48 the proportion of subjects with HIV RNA <50 copies/ml were 63%, 80% and 86% for the ZDV/3TC/ABC, ZDV/3TC/EFV and ZDV/3TC/ABC/EFV arms, respectively. The study Data Safety Monitoring Board stopped the ZDV/3TC/ABC arm at this time based on the higher proportion of patients with virologic failure. The remaining arms were continued in a blinded fashion. After a median follow-up of 144 weeks, 25% of subjects on the ZDV/3TC/ABC/EFV arm and 26% on the ZDV/3TC/EFV arm were categorised as having virological failure. There was no significant difference in the time to first virologic failure (p=0.73, log-rank test) between the 2 arms. In this study, addition of ABC to ZDV/3TC/EFV did not significantly improve efficacy.

		ZDV/3TC/ABC	ZDV/3TC/EFV	ZDV/3TC/ABC/EFV
Virologic failure (HIV RNA >200 copies/ml)	32 weeks	26%	16%	13%
	144 weeks	-	26%	25%
Virologic success (48 weeks HIV RNA < 50 copies/ml)		63%	80%	86%

- *Therapy experienced adults*

In adults moderately exposed to antiretroviral therapy the addition of abacavir to combination antiretroviral therapy provided modest benefits in reducing viral load (median change 0.44 $\log_{10}$ copies/ml at 16 weeks).

In heavily NRTI pretreated patients the efficacy of abacavir is very low. The degree of benefit as part of a new combination regimen will depend on the nature and duration of prior therapy which may have selected for HIV-1 variants with cross-resistance to abacavir.

Once daily (600 mg) administration:

- *Therapy naïve adults*

The once daily regimen of abacavir 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 - Centre for Disease Control and Prevention (CDC) stage A. They were randomised to receive either abacavir 600 mg once daily or 300 mg twice daily, in combination with efavirenz and lamivudine given once daily. 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. Long term data with abacavir used as a once daily regimen (beyond 48 weeks) are currently limited.

- *Therapy experienced adults*

In study CAL30001, 182 treatment-experienced patients with virologic failure were randomised and received treatment with either the fixed-dose combination of abacavir/lamivudine (FDC) 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. Results indicate that the FDC group was non-inferior to the abacavir twice daily group, based on similar reductions in HIV-1 RNA as measured by average area under the curve minus baseline (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%) 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 abacavir/lamivudine FDC plus a PI or NNRTI for 48 weeks.

Results indicate that the FDC 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).

Additional information:

The safety and efficacy of Ziagen in a number of different multidrug combination regimens is still not completely assessed (particularly in combination with NNRTIs).

Abacavir penetrates the cerebrospinal fluid (CSF) (see section 5.2), and has been shown to reduce HIV-1 RNA levels in the CSF. However, no effects on neuropsychological performance were seen when it was administered to patients with AIDS dementia complex.

Paediatric population:

A randomised comparison of a regimen including once daily vs 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 96 weeks. Of note, from this study clinical data were not available for children under one year old. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily n/N (%)	**Once Daily n/N (%)**
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/ml	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/ml	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	

Week 96		
Plasma HIV-1 RNA <80 c/ml	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

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 vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

In a separate study comparing the unblinded NRTI combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA ≤400 copies/ml at 48 weeks, compared with those treated with lamivudine and zidovudine (47%)[p=0.09, intention to treat analysis]. Similarly, greater proportions of children treated with the abacavir containing combinations had HIV-1 RNA ≤50 copies/ml at 48 weeks (53%, 42% and 28% respectively, p=0.07).

In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/ml at Week 48. No safety concerns were observed in these subjects.

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. Abacavir/Lamivudine is not recommended for use in patients with a creatinine clearance < 30 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) AUC value was 24.1 (10.4 to 54.8) µg.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, Abacavir/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. Abacavir/Lamivudine is not recommended for use in patients with a creatinine clearance < 30 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. Paediatric pharmacokinetic studies have demonstrated that once daily dosing provides equivalent AUC_{24} to twice daily dosing of the same total daily dose for both oral solution and tablet formulations.

The absolute bioavailability of lamivudine (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 AUC_{24} 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

Sodium starch glycolate (Type A)

Magnesium stearate

Tablet coat:

Hypromellose 2910 (3cp)

Hypromellose 2910 (6cp)

Titanium dioxide

Polysorbate 80

Macrogol 400

FD&C Yellow No.6 Aluminum lake (E110)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Blister pack: Store below 30ºC.

HDPE: The medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Abacavir/Lamivudine film-coated tablets are available in Clear PVC/PVdC-Aluminium blister packs and white opaque HDPE container closed with white opaque polypropylene closure.

Pack sizes:
Blister packs: 30, 50, 60, 90 film-coated tablets
HDPE packs: 30, 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited

Ares Block, Odyssey Business Park

West End Road

Ruislip HA4 6QD

United Kingdom

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