1. NAME OF THE MEDICINAL PRODUCT

Abacavir and Lamivudine Tablets USP, 600 mg/300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Abacavir Sulfate USP equivalent to Abacavir…600mg

Lamivudine USP …….300 mg

For Excipients see point 6.1

3. PHARMACEUTICAL Form

Tablet

Orange colored, modified capsule shaped, biconvex film coated tablets debossed with "I 60" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing at least 25 kg. Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

4.2 Posology and method of administration

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

Posology

Adults adolescents and children weighing at least 25 kg:

The recommended dose of Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets is one tablet once daily.

Children under 25 kg:

Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets should not be administered to children who weigh less than 25 kg because appropriate dose adjustments cannot be achieved with this product.

Special Populations

Elderly:

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

Dose adjustments:

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

Renal impairment:

Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets is not recommended for use in patients with a creatinine clearance < 50 ml/min as appropriate dose adjustments cannot be made.

Hepatic impairment:

No data are available in patients with moderate or severe hepatic impairment, therefore the use of Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets is not recommended unless judged necessary. In patients with mild hepatic impairment close monitoring is required

Method of administration

Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets 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.

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 these agents.

Hypersensitivity reactions

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

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

Therefore the following should be adhered to:

• HLA-B*5701 status must always be documented prior to initiating therapy.

• Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir containing regimen.

• Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets **must be stopped without delay**, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets after the onset of hypersensitivity may result in a life-threatening reaction.

• After stopping treatment with Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets for reasons of a suspected HSR, Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets **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 (as sulfate)/Lamivudine 600mg/300mg Tablets tablets

Clinical Description of abacavir HSR

Abacavir HSR has been well characterized through clinical studies and during post marketing followup.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. 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. Restarting abacavir in such patients must done in a setting where medical assistance is readily available.

Mitochondrial dysfunction

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 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.

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 abacavir or lamivudine treatment 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 (as sulfate)/Lamivudine 600mg/300mg Tablets might be higher than with other therapeutic options.

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 Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of 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 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) have also been reported to occur in the setting of immune reactivation;

however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Osteonecrosis

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

Opportunistic infections

Patients receiving abacavir or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by health care providers experienced in the treatment of these associated HIV diseases.

Transmission

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 relevant guidelines.

Liver disease

The safety and efficacy of Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets has not been established in patients with significant underlying liver disorders. Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets is not recommended in patients with moderate or severe hepatic impairment 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 (as sulfate)/Lamivudine 600mg/300mg Tablets 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.

Drug Interactions

Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets should not be taken with any other medicinal products containing lamivudine. Because of overlapping resistance and lack of additive antiretroviral effects, lamivudine should not be co-administered with emtricitabine. The combination of lamivudine with cladribine is not-recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets contains abacavir and lamivudine, therefore any interactions identified for these individually may occur with Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets. 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); coadministration of lamivudine with OCT inhibitors may increase lamivudine exposure. Abacavir and lamivudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P450 enzymes. Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets should not be taken with any other medicinal products containing lamivudine. 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 Didanosine/Lami	Interaction not studied.	No dosage adjustment necessary
Zidovudine/Lamivudine	Lamivudine: AUC ↔ Zidovudine : AUC ↔	No dosage adjustment necessary

Emtricitabine/Lamivudine		Due to similarities, Abacavir (as sulfate)/Lamivudine 600mg 300mg Tablets should not be administered concomitantly with other cytidine analogues, such as emtricitabine.
ANTI-INFECTIVE PRODUCTS		
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Abacavir	Interaction not studied.	No Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets dosage adjustment necessary. When concomitant administration with cotrimoxazole 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 (160mg/800mg once daily for 5 days/300mg 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.
Drugs by Therapeutic Area	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration

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 phenytoinconc entrations.
Phenytoin/Lamivudine	Interaction not studied.	
ANTIHISTAMINES (HISTAMINE H2 RECEPTOR ANTAGONISTS)		
Ranitidine/Abacavir	Interaction not studied.	No dosage adjustment necessary
Ranitidine/Lamivudine	Interaction not studied. necessary. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	No dosage adjustment necesarry
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.	No dosage adjustment necessary
Drugs by Therapeutic Area	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration
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	Concomitant use of lamivudine with cladribine is not recommended.
OPIOIDS		
Methadone/Abacavir (40 to 90mg once daily for 14 days/600mg single dose, then 600mg twice daily for 14 days)	Abacavir: AUC ↔ Cmax ↓35% Methadone: CL/F ↑22%	Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms and methadone doses should be adjusted accordingly.
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.	
ANTIVIRALS		
Lopinavir and ritonavir/abacavir:	In a pharmacokinetic study, co-administration of 600 mg abacavir once daily with lopinavir/ritonavir 400/100 mg twice daily led to a 32% decrease in abacavir plasma AUC. The clinical relevance of this is unknown.	Insufficient data to recommend dosage adjustment.

Drugs by Therapeutic Area	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration
Tipranavir and ritonavir/abacavir:	Co-administration of abacavir and tipranavir + ritonavir decreased the plasma AUC of abacavir by approximately 40%. The clinical relevance is unknown.	Insufficient data to recommend dosage adjustment.
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 (3.2g, 10.2g, 13.4g) / Lamivudine	Single dose lamivudine oral solution 300mg Lamivudine: AUC ↓ 14%; 32%; 36% Cmax ↓ 28%; 52%; 55%	When possible, avoid chronic co-administration of Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets 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 co-administration cannot be avoided.

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

4.6 Pregnancy and lactation

Pregnancy

No increased risk of birth defects has been reported for abacavir or lamivudine. However, risks to the fetus cannot be ruled out. Abacavir and lamivudine in combination should not be initiated during pregnancy, due to the risk of a hypersensitivity reaction to

abacavir. If a patient becomes pregnant during treatment with abacavir, however, this therapy may be continued if the benefit is considered to outweigh the risk.

Breast-feeding:

Abacavir and Lamivudine are excreted into human milk Current recommendations on HIV and breast-feeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility:

Studies in animals showed that neither abacavir nor lamivudine had any effect on fertility

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.

Nevertheless, the clinical status of the patient and the adverse reaction profile of abacavir and lamivudine should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Overview

The adverse reactions reported for Abacavir (as sulfate)/Lamivudine 600mg/300mg 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 reaction. If Abacavir (as sulfate)/Lamivudine 600mg/300mg has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart a medicinal product containing abacavir, the possibility of a hypersensitivity reaction should be borne in mind and these patients should be closely monitored for signs and symptoms 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.

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).

Blood and lymphatic system disorders

Common: anaemia, and leucopenia

Uncommon: neutropenia, 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

Nervous system disorders

Common: headache, insomnia, dizziness

Rare: paraesthesia, somnolence, loss of mental acuity, convulsions

Very rare: peripheral neuropathy

Respiratory, thoracic and mediastinal disorders

Common: cough, nasal symptoms

Uncommon: dyspnoea.

Gastrointestinal disorders

Common: nausea, vomiting, diarrhoea, abdominal pain

Rare: pancreatitis, rise in serum amylase,

Hepatobiliary disorders

Uncommon: raised blood levels of liver enzymes (AST, ALT)

Rare: hepatitis.

Skin and subcutaneous tissue disorders

Common: rash, alopecia

Rare: angioaedema

Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders

Common: arthralgia, muscle disorders

Rare: rhabdomyolysis

General disorders and administration site conditions

Common: fever, lethargy, fatigue, malaise

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 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 lifethreatening 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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment

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

Paediatric population

The safety database to support once daily dosing in paediatric patients comes from a study in which 669 HIV-1 infected paediatric subjects (from 12 months to ≤17 years old). Received abacavir and lamivudine either once or twice daily within this population, 104 HIV-1 infected paediatric subjects weighing at least 25 kg received abacavir and 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. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose:

No specific symptoms or signs have been identified following acute overdose with abacavir or lamivudine, apart from those listed as undesirable effects. If overdose occurs the patient should be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations,

ATC code: J05AR02

Mechanism of action

Abacavir and lamivudine are NRTIs. Both agents are metabolised sequentially by intracellular kinase to the respective 5′-triphosphate (TP). Lamivudine-TP and carbovir-TP (the active triphosphate form abacavir). They are competitive inhibitors of the reverse transcriptase (RT) of both HIV-1 and HIV-2Abacavir and lamivudine show significantly less affinity for host cell DNA polymerases. No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: didanosine, nevirapine and zidovudine). The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Clinical efficacy

Adults

Clinical experience with the combination of abacavir and lamivudine as a once daily regimen is mainly based on four studies in treatment-naïve subjects and two studies in treatment-experienced subjects, In antiretroviral therapy-naïve adult patients treated with abacavir 300 mg twice daily, together with lamivudine and efavirenz, the proportion of patients with plasma HIV-1 RNA 50 copies/ml by Week 48 was 70%, by intention-to-treat analysis. Though the clinical benefit of abacavir has otherwise mainly been demonstrated in combination with lamivudine and zidovudine, this triple nucleoside regimen is no longer recommended as a preferred treatment option, due to inferior efficacy compared to NNRTI- or PI-containing regimens

Children

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

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

Resistance

In the pivotal clinical trials, the most common mutation emerging in patients failing on abacavir containing regimens (also including lamivudine) was M184V/I. Other key mutations appearing, though more rarely, include L74V and K65R. When occurring together with M184V/I, either of these mutations substantially reduce the activity of abacavir. The presence of M184V with K65R gives rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. A further mutation selected for and reducing the activity of abacavir is Y115F. Though TAMs (M41L, D67N/G, K70R, L210W, T215F/Y, K219E/Q/N/R) are generally not selected for when failing on abacavir-containing regimens in the absence of thymidine analogues, the presence of two or more together with M184V will substantially reduce the activity of abacavir. In addition, the 69 insertion complex or the Q151M mutation cause a high level of resistance to abacavir. When combination antiretroviral therapy comprising lamivudine fails virologically, the M184V mutation will be selected for at an early stage (particularly if the regimen does not contain a boosted PI). M184V causes high-level resistance to lamivudine (>300-fold reduced susceptibility). In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The

clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered when the activity of the best available NRTI backbone is significantly compromised.

5.2 Pharmacokinetic properties

Absorption

Abacavir is rapidly absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83%. Following single dose administration of Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets in healthy volunteers, the mean (SD) abacavir C_{max} value was 5723 (1396) ng/ml, and the corresponding value for $AUC_{0\text{-}inf}$ was 17960 (4324) ng·hour/ml and $AUC_{0\text{-}t}$ was 17806 (4297) ng·hour/ml. The median (range) abacavir t_{max} value was 1.50 (0.75-4.0) hours.

Following single dose administration of Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets in healthy volunteers, the mean (SD) lamivudine C_{max} value was 2608 (732) ng/ml, and the corresponding value for $AUC_{0\text{–}inf}$ was 14864 (3311) ng·hour/ml and $AUC_{0\text{-}t}$ was 14605 (3320) ng·hour/ml. The median (range) lamivudine t_{max} value was 2.25 (0.75-5.0) hours.

Distribution

Following intravenous administration, the apparent volume of distribution with regards to abacavir and lamivudine was about 0.8 and 1.3l/kg respectively. Plasma protein binding of abacavir to human plasma proteins at therapeutic concentrations is ~49%. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited plasma protein binding (< 36%). Studies in HIV-infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%.

Metabolism

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. Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominantly cleared by renal excretion of unchanged lamivudine.

Elimination

The mean plasma 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 (as sulfate)/Lamivudine 600mg/300mg Tablets is not recommended for use in patients with a creatinine clearance < 50 ml/min as necessary dose adjustment cannot be made.

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

Special populations

Hepatic impairment:

There are no data available on the use of Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets in hepatically impaired patients. Pharmacokinetic data has been obtained for abacavir and lamivudine alone. Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. The results showed that there was a mean increase of 1.89-fold in the abacavir AUC, and 1.58-fold in the elimination half-life. No recommendation on dosage adjustments can be given for this patient population due to the substantial variability of abacavir exposure. Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

Renal impairment:

Pharmacokinetic data have been obtained for lamivudine and abacavir alone. Abacavir is primarily metabolised by the liver with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Abacavir (as sulfate)/Lamivudine 600mg/300mg Tablets is not recommended for use in patients with a creatinine clearance < 50 ml/min as necessary dose adjustment cannot be made.

Children:

Abacavir is rapidly and well absorbed from oral formulations when administered to children. Paediatric pharmacokinetic studies have demonstrated that once daily dosing provides equivalent AUC_{24} to twice daily dosing of the same total daily dose.

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.

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

5.3 Preclinical safety data

Mutagenicity and carcinogenicity

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but like many nucleoside analogues they show activity in the *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 longter 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 an in the liver, urinary bladder, lymph nodes and the subcutis of females. The majority of these tumors 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 tumor 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 carcinogenic potential in humans 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, auto induction 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 fetus in rats, but not in rabbits. These findings included decreased fetal body weight, fetal 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

Microcrystalline cellulose, Sodium starch glycolate Type A, Povidone, ,Colloidal silicon dioxide, Low-substituted hydroxypropyl cellulose, Magnesium stearate, Instacoat universal orange A05G32713 (HPMC 2910/Hypromellose, Polyethylene Glycol, Polysorbate 80, Titanium Dioxide, FD&C Yellow No. 6 Al. Lake).

6.2 Incompatibilities

None

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

Blister pack: Plain 25 Micron Aluminium Foil/6-8 gsm HSL with Cold Form Laminate (25µ OPA / 45µ ALU /60µ PVC).

Blister pack of 6 Tablets, such 10 blisters along with pack insert in a box.

Container Pack: Round, white, HDPE, 75 CC HW, 38 mm neck finish container with 38 mm Child resistant closure with pulp and HS white printed liner along with 1 gm carbon/silica blend sachet (One Pillow pack per container).

Container pack of 30’s Tablets along with pack insert in a box.

6.6 Special Precaution for disposal

No special requirements.

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

7. Marketing Authorization Holder

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9. DATE OF <PREQUALIFICATION>/<RENEWAL OF PREQUALIFICATION>

10. DATE OF REVISION OF THE TEXT

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