SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated dispersible tablet contains 120 mg abacavir (as sulfate) and 60 mg lamivudine.

Excipient with known effect

Each dispersible tablet contains 12 mg aspartame.For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

White to off white capsule shaped, biconvex, uncoated tablet debossed with “CJ” on one side and deepscoreline on other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in children (see also section 4.4 concerning abacavir (as sulfate)/lamivudine dispersible tablets use and HLA- B*5701 screening).

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO).

This product is intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

4.2. Posology and method of administration

Posology

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

Children 6 weeks of age and above

Number of tablets by weight band to be taken twice daily (approximately 12 hours apart) or once daily.

Body weight	Recommended number of tablets	
	Twice daily dosing (morning and evening)	**Once daily dosing**
3- 5.9 kg	½ tablet	1 tablet
6- 9.9 kg	½ tablet in the morning and 1 tablet in the evening	1 and ½ tablets
10-13.9 kg	1 tablet	2 tablets
14-19.9 kg	1 tablet in the morning and 1 ½ tablet in the evening	2 and ½ tablets
20-24.9 kg	1½ tablets	3 tablets

For very young children who cannot swallow tablets, abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg should be dispersed in water before administration. Please use the following procedure to disperse abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg:

1. The number of tablets to be administered to each patient will be determined by his or her bodyweight (as shown in table above).
2. Remove the number of tablets recommended for one dose from the bottle with dry hands
3. Place the tablet(s) in a container and add two teaspoonfuls (10 ml) of drinking water per tablet.
4. Swirl or stir until the tablets disperse completely. The suspension has a strawberry flavour.
5. The child should consume the entire quantity immediately.
6. Rinse the container with an additional small amount of drinking water and let the child drinkthe contents to assure that the whole dose is taken.
7. Do not mix the tablets with any liquid other than water.

Children weighing 25 kg or more, adolescents and adults

For these patient groups other formulations with higher amounts of the active substances are available. Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg can be taken with or without food.

Dose adjustments

Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg is a fixed-dose tablet and should not be prescribed for patients requiring dose 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 healthcare provider should refer to the product information of the individual medicinal products.

Renal impairment: Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg is not recommended for use in patients with a creatinine clearance < 50 ml/min (see section 5.2), as

appropriate dose adjustments are not possible. For such patients, separate formulations of abacavir and lamivudine should be used.

Hepatic impairment: Abacavir is primarily metabolised by the liver. No clinical data are available in patients with moderate hepatic impairment, therefore the use of abacavir (as sulfate)/ lamivudine dispersible tablets 120mg/60mg is not recommended unless judged necessary. In patients with mild and moderate hepatic impairment close monitoring is required (see sections 4.4 and 5.2). Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg is contraindicated in patients with severe hepatic impairment (see section 4.3).

Method of administration

For oral use.

4.3. Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. See BOXED INFORMATION ON ABACAVIR HYPERSENSITIVITY REACTIONS in section 4.4 and section 4.8.

Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg is contraindicated in patients

- with severe hepatic impairment.

4.4. Special warnings and precautions for use

The special warnings and precautions relevant to abacavir and lamivudine are included in thissection. There are no additional precautions and warnings relevant to the combination of these agents.

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

Hypersensitivity reaction (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.

In a clinical study, 3.4 % of subjects with a negative HLA-B*5701 status receiving abacavir developed a hypersensitivity reaction. Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. In a prospective study, use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele significantly reduced the incidence of abacavir hypersensitivity reactions. In populations similar to that enrolled in this study, it is estimated that 48% to 61% of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with

0% to 4% of patients who do not have the HLA-B*5701 allele. These results are consistent with those of prior retrospective studies.

As a consequence, screening for carriage of the HLA-B*5701 allele is recommended in any HIV infected patient without prior exposure to abacavir. Overall frequencies of hypersensitivity reactions have been reported to vary across different racial groups (e.g. lower frequency in African Americans and black Africans). Nevertheless, screening for HLA-B*5701 should be performed in any patient irrespective of race. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see “Management after an interruption of abacavir therapy”). Abacavir should not be used in patients known to carry the HLAB*5701 allele. Only in the rare case where no other therapeutic option is available based on the treatment history, drug tolerability and resistance testing, the use of abacavir might be considered. However, such patients must be very closely monitored for signs and symptoms of a hypersensitivity reaction.

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. Therefore, even in the absence of the HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds. This is due to the potential for asevere or even fatal reaction.

Skin patch testing is not a tool for prospectively evaluating abacavir tolerability in abacavir-naïve patients. It has not been thoroughly evaluated for use in routine clinical management of patients, and should not be used as a substitute for genotyping for HLA-B*5701.

Clinical Description

Hypersensitivity reactions are characterised by the appearance of symptoms indicating multi-organ system involvement. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome.

Other signs and symptoms may include respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised), gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia). The symptoms related to this hypersensitivity reaction worsen with continued therapy and can be life- threatening. These symptoms usually resolve upon discontinuation of abacavir.

Clinical Management

Hypersensitivity reaction symptoms usually appear within the first six weeks of initiation of treatment with abacavir, although these reactions may occur at any time during therapy. Patients should be monitored closely, especially during the first two months of treatment with abacavir, with consultation every two weeks.

Patients who are diagnosed with a hypersensitivity reaction whilst on therapy MUST discontinue abacavir immediately.

Abacavir, MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction**.** Restarting abacavir following a hypersensitivity reaction results 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.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, abacavir must be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medicinal products).

Special care is needed for those patients simultaneously starting treatment with abacavir and other medicinal products known to induce skin toxicity (such as non-nucleoside reverse transcriptase inhibitors - NNRTIs). This is because it is currently difficult to differentiate between rashes induced by these products and abacavir related hypersensitivity reactions.

Management after an interruption of abacavir therapy

Regardless of a patient's HLA-B*5701 status, if therapy with abacavir has been discontinued for any reason and restarting therapy is under consideration, the reason for discontinuation must be established to assess whether the patient had any symptoms of a hypersensitivity reaction. If a hypersensitivity reaction cannot be ruled out, abacavir must not be restarted.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping abacavir. The most common isolated symptom of a hypersensitivity reaction was a skinrash.

Moreover, on very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction (i.e. patients previously considered to be abacavir tolerant). In both cases if a decision is made to restart abacavir thismust be done in a setting where medical assistance is readily available.

Screening for carriage of the HLA B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir in such patients who test positive for the HLA B*5701 allele is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and withclose medical supervision.

Essential patient information

Healthcare providers must ensure that patients are fully informed regarding the following informationon the hypersensitivity reaction:

- patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that mayresult in a life-threatening reaction or death
- patients developing signs or symptoms possibly linked to a hypersensitivity reaction MUST CONTACT their healthcare provider IMMEDIATELY.
- patients who are hypersensitive to abacavir should be reminded that they must never take abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg or any other medicinal product containing abacavir (e.g. abacavir tablets, abacavir/dolutegravir/lamivudine tablets, abacavir/ lamivudine/zidovudine tablets).

- in order to avoid restarting abacavir, patients who have experienced a hypersensitivity reaction should be asked to return the remaining abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg to the pharmacy.
- patients who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their healthcare provider before restarting.
- each patient should be reminded to read the Patient Information Leaflet included in the abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

Lactic acidosis

Lactic acidosis is a rare but severe, potentially life-threatening complication associated with use of nucleoside reverse transcriptase inhibitors (NRTI). Several other agents of this class are known to cause lactic acidosis. Whereas this has not clearly been shown for abacavir, an association cannot be excluded. Lactic acidosis may occur after a few to several months of NRTI treatment.

Patients with hyperlactataemia may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnoea, fatigue, nausea, vomiting, diarrhoea and abdominal pain. Risk factors for NRTI- related lactic acidosis include female gender and obesity. Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may be at higher risk. Patients at increased risk should be closely monitored clinically. Screening for hyperlactataemia in asymptomatic patients treated with NRTIs, however, is not recommended. Symptomatic patients usually have levels > 5 mmol/l and require discontinuation of all NRTIs. Lactic acid levels > 10 mmol/l usually are a medical emergency.

Mitochondrial dysfunction following exposure *in utero*

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 postnatally to nucleoside analogues. The main adverse events reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV-infected patients. Whereas for some other antiretrovirals there is considerable evidence for this adverse reaction, the evidence for abacavir and lamivudine as causative agents is weak; indeed switching from a thymidine analogue to abacavir has been shown to increase limb fat in patients with lipoatrophy. A higher risk of lipodystrophy has been associated e.g. with older age of the patient, longer duration of antiretroviral therapy and related metabolic disturbances. Clinical examination should include evaluation for physical signs of fat

redistribution. Measurement of fasting serum lipids and blood glucose as well as appropriate management of lipid disorders should be considered (see section 4.8).

Pancreatitis

Pancreatitis has been reported, but a causal relationship to abacavir or lamivudine treatment is uncertain (see section 4.8). Treatment with abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Myocardial infarction

Published prospective, observational, epidemiological studies in adults have shown an association between myocardial infarction and the use of abacavir. A pooled analysis of 26 randomised controlled trials with over 5000 patients assigned to abacavir found no association between abacavir use and MI risk. There is no established biological mechanism to explain a potential increase in risk. Hence, the available data is overall inconclusive. When prescribing abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg, 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, 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 combination antiretroviral therapy. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and 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 combination antiretroviral therapy. 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 (as sulfate)/lamivudine dispersible tablets 120mg/60mg 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 healthcare 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

Caution should be exercised when administering lamivudine to any patient with hepatitis B coinfection. Lamivudine is a potent inhibitor of hepatitis B virus (HBV) replication. Discontinuation of lamivudine or virologic failure after development of resistance to lamivudine by HBV may cause hepatic deterioration and a hepatitis flare. Periodic monitoring of liver function tests and markers of HBV replication is recommended for at least four months if lamivudine is discontinued in HBV coinfected patients.

The safety and efficacy of abacavir has not been established in patients with significant underlying liver disorders. Clinical safety data with abacavir in patients with mild hepatic impairment is very limited and pharmacokinetic data show substantial variability of drug exposure in this population. Therefore, close safety monitoring is required.

No data are available in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to substantially increase in these patients. Therefore, the use of abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg in patients with moderate hepatic impairment is not recommended unless judged necessary and requires close monitoring of these patients. For patients with severe hepatic impairment, abacavir (as sulfate)/ lamivudine dispersible tablets 120mg/60mg is contraindicated (see section 4.3).

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 events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

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.

Important information about some of the other ingredients of abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg

Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg contain aspartame which is a source of phenylalanine. This may be harmful for people with phenylketonuria.

4.5. Interaction with other medicinal products and other forms of interaction

Abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg contains abacavir and lamivudine, therefore any interactions identified for these individually may occur with abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg. Clinical studies have shown that there are no clinically significant interactions between abacavir andlamivudine.

Based on the results of in vitro experiments and the known major metabolic pathways of abacavir, the potential for cytochrome P450 mediated interactions with other medicinal products involving abacavir are low. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Lamivudine does not inhibit the cytochrome P450 isoform CYP3A.

Interaction studies have only been performed in adults. 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
ANTI-INFECTIVE PRODUCTS		
Trimethoprim / sulfamethoxazole (Co-trimoxazole)/Abacavir	Interaction not studied.	No abacavir (as sulfate)/ lamivudine dispersible tablets 120mg/60mg 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)	

Drugs by Therapeutic Area	Interaction Geometric mean change (%)(Possible mechanism)	Recommendation concerning co-administration
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. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment. Monitor phenytoin concentrations.
Phenytoin/Lamivudine	Interaction not studied.	
ANTIHISTAMINES (HISTAMINE H2 RECEPTOR ANTAGONISTS)		
Ranitidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
Ranitidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	
Cimetidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.

Drugs by Therapeutic Area	Interaction Geometric mean change (%)(Possible mechanism)	Recommendation concerning co-administration
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 ↔ Cmax ↓35% Methadone: CL/F ↑22%	No abacavir (as sulfate)/ lamivudine dispersible tablets 120mg/60mg dosage adjustment necessary. Methadone dosage

Methadone/Lamivudine	Interaction not studied.	methadone dosage adjustment unlikely in majority of patients; occasionally methadone re- titration may be required.

Drugs by Therapeutic Area	Interaction Geometric mean change (%)(Possible mechanism)	Recommendation concerning co-administration
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	Interaction not studied.	
ANTIRETROVIRALS		
Didanosine/Abacavir	Interaction not studied	No dosage adjustment necessary
Didanosine/Lamivudine	Interaction not studied	
Zidovudine/Abacavir	Interaction not studied	
Zidovudine/Lamivudine Zidovudine 300mg single dose Lamivudine 150mg single dose	Lamivudine: AUC ↔ Zidovudine: AUC ↔	
Emtricitabine/Lamivudine		Due to similarities, abacavir (as sulfate)/lamivudine dispersible tablets 120mg/ 60mg should not be administered concomitantly with other cytidine analogues, such as emtricitabine
Lopinavir and ritonavir/ abacavir:	In a pharmacokinetic study, coadministration 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 ofthis is unknown.	Insufficient data to recommend dosage adjustment.

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.

Drugs by Therapeutic Area	Interaction Geometric mean change (%)(Possible mechanism)	Recommendation concerning co-administration
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.	

Abbreviations: ↑ = Increase; ↓=decrease; ↔= no significant change; AUC=area under the concentrationversus time curve; C_{max}=maximum observed concentration; CL/F=apparent oralclearance

Potent enzymatic inducers such as rifampicin, phenobarbital and phenytoin may, via their effects on UDP-glucuronyl transferases, decrease the plasma concentrations of abacavir. The magnitude of any such effects, as well as their possible clinical consequences, are unknown.

4.6. Fertility, Pregnancy and lactation

Pregnancy

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

Animal studies with abacavir have shown toxicity to the developing embryo and foetus in rats, but not in rabbits. Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats. (see section 5.3). The active ingredients of abacavir (as sulfate)/ lamivudine dispersible tablets 120mg/60mg may inhibit cellular DNA replication and abacavir has been shown to be carcinogenic in animal models (see section 5.3). The clinical relevance of these findings is unknown. Placental transfer of abacavir and lamivudine has been shown to occur in humans.

In pregnant women treated with abacavir, more than 800 outcomes after first trimester exposure and more than 1000 outcomes after second and third trimester exposure indicate no malformative and foetal/neonatal effect. In pregnant women treated with lamivudine, more than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure indicate no malformative and foetal/neonatal effect. There are no data on the use of abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg in pregnancy, however the malformative risk is unlikely in humans based on those data.

For patients co-infected with hepatitis who are being treated with a lamivudine containing medicinal product such as abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV- negative infants exposed *in utero* and/or post-natally to nucleoside analogues (see section 4.4).

Breastfeeding

Lamivudine and abacavir, are excreted into the breast milk of lactatingmothers.

Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age.

Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter.

Preferred options may vary depending on the local circumstances.Fertility

Studies in animals showed that neither abacavir nor lamivudine had any effect on fertility (see section5.3).

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. 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 dispersible tablets 120mg/ 60mg 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.

Abacavir hypersensitivity (see also section 4.4)

In a clinical study, 3.4 % of subjects with a negative HLA-B*5701 status receiving abacavir developeda hypersensitivity reaction.

Some hypersensitivity reactions were life-threatening and resulted in fatal outcome despite taking precautions (see also section 4.4). This reaction is characterised by the appearance of symptoms indicating multiorgan/body-system involvement.

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 orfever.

The signs and symptoms of this hypersensitivity reaction are listed below. These have beenidentified either from clinical studies or post marketing surveillance. Those reported **in at least 10% of patients**with a hypersensitivity reaction are in bold text.

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
Rash (81% vs 67% respectively) and gastrointestinal manifestations (70% vs 54% respectively) weremore frequently reported in children compared to adults.

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. This delay in diagnosis of hypersensitivity has resulted in abacavir being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases.

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. Close medical supervision is necessary during the first two months, with consultations every twoweeks.

It has been suggested that intermittent therapy may increase the risk of developing clinically significant hypersensitivity reactions. Consequently, patients should be advised of the importance of taking abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg regularly.

Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction is usually more severe than on initial presentation, and may include life-threatening hypotension and death.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity prior to stopping abacavir. The most common isolated symptom of a hypersensitivity reaction was a skin rash. On very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction. In both cases, if a decision is made to restart abacavir this must be done in a setting where medical assistance is readily available.

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 dispersible tablets 120mg/60mg 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 (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.

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). Care must be taken to eliminate the possibility of a hypersensitivity reaction if anyof these symptoms occur.

Body system	Abacavir	Lamivudine
Blood and lymphatic systems disorders		*Uncommon*: neutropenia and anaemia (both occasionally severe), thrombocytopenia *Very rare*: pure red cell aplasia
Immune system disorders	*Common*: hypersensitivity	
Metabolism and nutritiondisorders	*Common*: anorexia *Very rare*: lactic acidosis	Very rare: lactic acidosis
Nervous system disorders	*Commøn*: headache	*Common*: headache, insomnia. *Very rare*: cases of peripheral neuropathy (or paraesthesia) have been reported

Respiratory, thoracic andmediastinal disorders		*Common:* cough, nasalsymptoms

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 tissuedisorders	*Common:* rash (without systemicsymptoms) *Very rare:* erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	*Common*: rash, alopecia *Rare:* angiodema
Musculoskeletal and connectivetissue disorders		*Common:* arthralgia, muscledisorders *Rare:* rhabdomyolysis
General disorders and administration site conditions	*Common*: fever, lethargy, fatigue.	*Common:* fatigue, malaise, fever.

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 (as sulfate)/lamivudine dispersible tablets 120mg/60mg 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 are important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the marketing authorization holder, or, if available, via the TMDA ADR reporting tool; website: https://imis.tmda.go.tz/arrt or search for TMDA Adverse Reactions Reporting Tool in the Google Play Store";

4.9. Overdose

No specific symptoms or signs have been identified following acute overdose with abacavir orlamivudine, 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 dialyzable, 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, and are potent selective inhibitors of HIV-1 and HIV-2 (LAV2 and EHO) replication. Both agents are metabolised sequentially by intracellular kinases to the respective 5′-triphosphate (TP) which are the active moieties. Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: didanosine, nevirapine and zidovudine). The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Clinical efficacy

Adults

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 (see section 4.4).

Paediatric population

A comparison of a regimen including once daily versus twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least an additional 96 weeks. Within this population, 104 patients, weighing at least 25 kg, received 600 mg abacavir and 300 mg lamivudine as abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg once daily, with a median duration of exposure of 596 days.

Among the 669 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%, for the primary endpoint of <80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested

(<200c/mL, <400c/mL, <1000c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once versus twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysismethod.

Among the 104 patients who received abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg, including the ones who were between 40 kg and 25 kg, the viral suppression was similar.

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.

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 boostedPI). 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 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.

Following single dose administration of abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg, in healthy volunteers, the mean (± SD) abacavir C_{max} value was 5838 (± 2023) ng/ml, and the corresponding value for AUC was 15059 (± 2456) ng.h/ml. The mean (± SD) abacavir t_{max} value was 0.80 (± 0.59) hours. The mean (± SD) lamivudine C_{max} value was 2868 (± 689) ng/ml and the corresponding value for AUC was 14280 (± 3297) ng.h/ml. The mean (± SD) lamivudine t_{max} values was 1.86 (± 0.84) hours.

Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore abacavir (as sulfate)/lamivudine dispersible tablets 120mg/60mg, can be taken with or without food.

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.

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. 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 (as sulfate)/lamivudine dispersible tablets 120mg/60mg is not recommended for use in patients with a creatinine clearance < 50 ml/min as necessary dose adjustment cannot be made (see section 4.2).

Intracellular pharmacokinetics

In a study of 20 HIV-infected patients receiving abacavir 300 mg twice daily, with only one 300 mg dose taken prior to the 24 hour sampling period, the geometric mean terminal carbovir-TP intracellular

half-life at steady-state was 20.6 hours, compared to the geometric mean abacavir plasma half-life in this study of 2.6 hours. In a crossover study in 27 HIV-infected patients, intracellular carbovir-TP exposures were higher for the abacavir 600 mg once daily regimen ($AUC_{24,ss}$ + 32 %, $C_{max24,ss}$ + 99 % and C_{trough} + 18 %) compared to the 300 mg twice daily regimen. For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16-19 hours, compared to the plasma lamivudine half-life of 5-7 hours. In a crossover study in 60 healthy volunteers, intracellular lamivudine-TP pharmacokinetic parameters were similar ($AUC_{24,ss}$ and $C_{max24,ss}$) or lower (C_{trough} – 24%) for the lamivudine 300 mg once daily regimen compared to the lamivudine 150 mg twice daily regimen. Overall, these data support the use of lamivudine 300 mg and abacavir 600 mg once daily for the treatment of HIV-infected patients. Additionally, the efficacy and safety of this combination given once daily has been demonstrated in a pivotal clinical study (CNA30021)

Special population

Hepatic impairment

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. No pharmacokinetic data are available for patients with moderate to severe hepatic impairment (see section 4.2 and 4.4).

Renal impairment

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 dispersible tablets 120mg/60mg 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 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.

There are insufficient data to recommend the use of abacavir in infants less than six weeks old.

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

5.3. Preclinical safety data

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

Mutagenicity and carcinogenicity

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but like many 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 testedconcentrations.

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 glandof 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 the 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 femalefertility.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose,Sodium starch glycolate, Hypromellose,
Corn starch,
Strawberry cream flavour,Aspartame,
Colloidal silicon dioxide,Magnesium stearate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months (60s pack)36 months (30s pack)

6.4. Special precautions for storage

Do not store above 30°C.

6.5. Nature and contents of container

Tablets are packed in 85cc HDPE container with 38 mm CRC polypropylene cap, having a silica gelbag of 1g and rayon sanicoil. Pack size: 60 tablets

Tablets are packed in 50cc HDPE container with 38 mm CRC polypropylene cap, having a silica gelbag of 1g and rayon sanicoil. Pack size: 30 tablets

6.6. Instructions for use and handling and disposal

No special requirements.

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

7. Marketing authorization holder

Cipla LimitedCipla House,
Peninsula Business Park
Ganpatrao Kadam Marg, Lower ParelMumbai -400013,
India
Phone: 9122 24826000
Fax: 91-22-24826120

8. Marketing authorization number

TAN 21 HM 0345

9. Date of first authorization/renewal of the authorisation

2021-08-20

10. DATE OF REVISION OF THE TEXT