SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

DUMIVA DISPERSIBLE TABLETS (120 mg/60 mg, dispersible tablets)

WARNING:

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE SECTION 4.4).

Hypersensitivity reaction:

Skin patch testing has no utility in the clinical management of patients and therefore should not be used in the clinical setting.

Before initiating treatment with DUMIVA DISPERSIBLE TABLETS, screening for carriage of the HLA-B*5701 allele should be performed. DUMIVA DISPERSIBLE TABLETS should not be used in patients known to carry the HLA-B*5701 allele.

In clinical studies approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction. Some of these cases were life-threatening and resulted in a fatal outcome despite taking precautions.

Studies have shown that carriage of the HLA-B*5701 allele is associated with a more than 50 % increased risk of a hypersensitivity reaction to abacavir.

Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available based on the treatment history and resistance testing.

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

- **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 DUMIVA DISPERSIBLE TABLETS.

- **<u>Clinical management:</u>**

Hypersensitivity reaction symptoms usually appear within the first six weeks of initiation of treatment with DUMIVA DISPERSIBLE TABLETS, although these reactions may occur at any time during therapy. Patients should be monitored closely, especially during the first two months of treatment with DUMIVA DISPERSIBLE TABLETS, with consultation every two weeks. Patients who are diagnosed with a hypersensitivity reaction whilst on therapy MUST discontinue the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS immediately.

The fixed-dose combination of DUMIVA DISPERSIBLE TABLETS, or any other medicine containing abacavir, MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction.

Restarting DUMIVA DISPERSIBLE TABLETS, or other medicines containing 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, the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS 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 medicines).

Special care is needed for those patients simultaneously starting treatment with the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS and other medicines known to induce skin toxicity (such as nucleotide and 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.

- **<u>Management after an interruption of the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS therapy:</u>**

If therapy with the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS 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, the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS or any other medicines containing 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 skin rash. 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. In both cases if a decision is made to restart abacavir this must be done in a setting where medical assistance is readily available.

- **<u>Essential patient information:</u>**

Prescribers must ensure that patients are fully informed regarding the following information on the hypersensitivity reaction:

- **Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir as in DUMIVA DISPERSIBLE TABLETS that may result in a life-threatening reaction or death.**
- **Patients developing signs or symptoms possibly linked with a hypersensitivity reaction**

MUST CONTACT their doctor IMMEDIATELY.

- **Patients who are hypersensitive to abacavir should be reminded that they must never take the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS or any other medicines containing abacavir again.**
- **In order to avoid restarting abacavir, patients who have experienced a hypersensitivity reaction should dispose of their remaining fixed-dose combination of DUMIVA DISPERSIBLE TABLETS in their possession in accordance with the local requirements and ask their doctor or pharmacist for advice.**
- **Patients who have stopped the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.**
- **Patients should be advised of the importance of taking the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS regularly.**
- **Each patient should be reminded to read the Patient Information Leaflet included in the fixed-dose combination of DUMIVA DISPERSIBLE TABLETS package.**
- **They should be reminded of the importance of removing the Alert Card included in the package and keep it with them at all time.**

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains:

Abacavir sulfate equivalent to abacavir 120 mg

Lamivudine 60 mg

Contains sweetener: Aspartame 15 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersible tablet

White to off-white, round, biconvex tablet with a criss-cross score on both sides of the tablet and debossed with “M” on the top left of the score over “A” on the bottom left of the score and “L” on the

bottom right of the score on one side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DUMIVA DISPERSIBLE TABLETS is a fixed-dose combination of two nucleoside analogues (abacavir and lamivudine).

DUMIVA DISPERSIBLE TABLETS are indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in children from three months to 12 years.

4.2 Posology and method of administration

Posology

- Patients should be stabilised on individual medicines before being switched over to DUMIVA DISPERSIBLE TABLETS.
- Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.
- DUMIVA DISPERSIBLE TABLETS can be taken with or without food (see section 5.2).
- DUMIVA DISPERSIBLE TABLETS may be crushed and mixed with a small amount of water or food and ingested immediately.

Children 3 months to 12 years

The recommended dose of DUMIVA DISPERSIBLE TABLETS based on body weight is as follows:

Child's weight	**Number of DUMIVA DISPERSIBLE TABLETS**
3 – 5,9 kg	1 tablet daily
6 – 9,9 kg	1,5 tablets daily
10 – 13,9 kg	2 tablets daily
14 – 19,9 kg	2,5 tablets daily
20 – 24,9 kg	3 tablets daily

Children weighing 25 kg or more, adolescents and adults

For these patient groups other fixed dose formulations with higher amounts of the active substances are available.

Special populations

DUMIVA DISPERSIBLE TABLETS is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance less than 50 mL/min or with mild hepatic impairment.

Separate preparations of abacavir or lamivudine should be administered in cases where discontinuation or dose adjustment is indicated.

In these cases, the medical practitioner should refer to the individual product information for these medicines.

Elderly

The pharmacokinetics of abacavir and lamivudine have not been studied in patients over 65 years of age and consideration must be given to the greater frequency of decreased hepatic, renal and cardiac function; concomitant medicines or disease.

Renal impairment

Whilst no dosage adjustment of abacavir is necessary in patients with renal dysfunction, a dose reduction of lamivudine is required due to decreased clearance.

DUMIVA DISPERSIBLE TABLETS is not recommended for use in patients with a creatinine clearance less than 50 mL/min.

Hepatic impairment

A dose reduction of abacavir is likely to be required for patients with mild hepatic impairment.

As dose reduction is not possible with DUMIVA DISPERSIBLE TABLETS the separate preparations should be used when judged necessary.

DUMIVA DISPERSIBLE TABLETS must not be used in patients with moderate and severe hepatic impairment.

Method of administration

For oral use.

4.3 Contraindications

DUMIVA DISPERSIBLE TABLETS is contraindicated in patients:

- With known hypersensitivity to abacavir, lamivudine, or to any of the excipients (for abacavir

hypersensitivity, (see section 6.1).

- With abnormally low neutrophil counts (< 0,75 x 109/L) (see section 4.4).
- With abnormally low haemoglobin levels (< 7,5 g/dL or 4,65 mmol/L) (see section 4.4).
- With severe hepatic impairment.
- With severe renal impairment.
- Who are receiving treatment with emtricitabine.
- Who are pregnant and breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Before initiating treatment with DUMIVA DISPERSIBLE TABLETS, screening for carriage of the HLA-B*5701 allele is advisable in any HIV-infected patient, irrespective of racial origin.

Screening is also recommended prior to re-initiation of DUMIVA DISPERSIBLE TABLETS in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see “Management after an interruption of DUMIVA DISPERSIBLE TABLETS therapy”).

DUMIVA DISPERSIBLE TABLETS should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.

Patients who develop a hypersensitivity reaction must discontinue DUMIVA DISPERSIBLE TABLETS and MUST not be re-challenged with DUMIVA DISPERSIBLE TABLETS.

Hypersensitivity reaction

- The warnings and special precautions relevant to both abacavir and lamivudine are included in this section.
- There are no additional special warnings and precautions relevant to DUMIVA DISPERSIBLE TABLETS.

Hypersensitivity to abacavir (see section 4.8)

In clinical studies, approximately 5 % of subjects receiving abacavir developed a hypersensitive reaction, which in rare cases has proved fatal.

Hypersensitivity is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

Patients who develop a hypersensitivity reaction must discontinue DUMIVA DISPERSIBLE TABLETS and MUST NOT be rechallenged with DUMIVA DISPERSIBLE TABLETS or any other product containing abacavir (see section 4.8).

Lactic acidosis / hyperlactataemia

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection.

Long-term use of DUMIVA DISPERSIBLE TABLETS can result in potentially fatal lactic acidosis.

Symptomatic hyperlactataemia and lactic acidosis are uncommon.

Suspicious biochemical features include raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

Use of DUMIVA DISPERSIBLE TABLETS can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/L) and the serum bicarbonate and respond as follows:

- Lactate 2 – 5 mmol/L with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5 – 10 mmol/L with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate > 10 mmol/L: STOP all therapy (80 % mortality).

The above lactate values may not be applicable to paediatric patients.

Caution should be exercised when administering DUMIVA DISPERSIBLE TABLETS to patients with known risk factors for liver disease and hepatic steatosis (including certain medicines and alcohol).

Treatment with DUMIVA DISPERSIBLE TABLETS should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion

gap and raised lactate level. Therapy should be stopped in any patient with a raised lactate level.

Blood for lactate assay should be heparinised and stored on ice. After recovery, NRTIs should be avoided.

Seek expert advice on medicine selection.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of DUMIVA DISPERSIBLE TABLETS alone or in combination.

Caution should be exercised when administering DUMIVA DISPERSIBLE TABLETS to any patient with hepatomegaly, hepatitis or other known risk factors of liver disease and hepatic steatosis (including certain medicines and alcohol).

Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

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. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Cardiovascular events

Although the available data from clinical and observational studies with abacavir show inconsistent results, several studies suggest an increased risk of cardiovascular events (notably myocardial infarction) in patients treated with abacavir. Therefore, when prescribing DUMIVA DISPERSIBLE TABLETS, action should be taken to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

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

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

The long-term consequences of these events are currently unknown.

Knowledge about the mechanism is incomplete.

A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised.

A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicine related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances.

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported, but a causal relationship to lamivudine and abacavir is uncertain. Pancreatitis has been observed in some patients receiving DUMIVA DISPERSIBLE TABLETS. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of DUMIVA DISPERSIBLE TABLETS until diagnosis of pancreatitis is excluded.

Patients with moderate to severe renal impairment

In patients with moderate to severe renal impairment, the terminal half-life of DUMIVA DISPERSIBLE TABLETS is increased due to decreased clearance. The dose of DUMIVA DISPERSIBLE TABLETS

should therefore be adjusted (see section 4.2).

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.

Liver disease

Use of DUMIVA DISPERSIBLE TABLETS can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of DUMIVA DISPERSIBLE TABLETS has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines. 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. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

The safety and efficacy of DUMIVA DISPERSIBLE TABLETS has not been established in patients with significant underlying liver disorders.

DUMIVA DISPERSIBLE TABLETS is contraindicated in patients with severe hepatic impairment.

Caution is advised when used in patients with hepatitis B.

Patients with HIV and hepatitis B or C virus co-infection

If lamivudine is being used concomitantly for the treatment of HIV and HBV, additional information relating to the use of lamivudine in the treatment of hepatitis B infection can be found in the Product Information of such products.

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.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines. Patients co-infected with HIV and HBV who discontinue DUMIVA DISPERSIBLE TABLETS should be closely

monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

If DUMIVA DISPERSIBLE TABLETS is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis (see the Product Information for such products).

Discontinuation of DUMIVA DISPERSIBLE TABLETS therapy in patients co- infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Severe hepatomegaly with steatosis

Particular caution should be exercised when administering DUMIVA DISPERSIBLE TABLETS to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors.

Treatment with DUMIVA DISPERSIBLE TABLETS should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues.

Immune Reconstitution Inflammatory

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks.

Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Relevant examples are cytomegalovirus retinitis (see paragraph above), generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary.

Osteonecrosis

Although the aetiology 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 (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving DUMIVA DISPERSIBLE TABLETS should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by health care professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

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.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including DUMIVA DISPERSIBLE TABLETS does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Important information about some of the ingredients of DUMIVA DISPERSIBLE TABLETS

DUMIVA DISPERSIBLE TABLETS contain aspartame which is a source of phenylalanine. This may be harmful for people with phenylketonuria.

4.5 Interaction with other medicines and other forms of interaction

DUMIVA DISPERSIBLE TABLETS contain abacavir and lamivudine therefore any interactions identified for these individually are relevant to DUMIVA DISPERSIBLE TABLETS.

Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine.

Abacavir and lamivudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system.

Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicines metabolised by major P450 enzymes.

The interactions listed below should not be considered exhaustive but are representative of the classes of medicines where caution should be exercised.

Interactions relevant to abacavir

Potent enzymatic inducers such as rifampicin, phenobarbital and phenytoin may via their action on UDP-glucuronyl transferases slightly decrease the plasma concentrations of abacavir.

Ethanol

The metabolism of abacavir is altered by concomitant consumption of ethanol resulting in an increase in AUC of abacavir of about 41 %.

These findings are not considered clinically significant.

Abacavir has no effect on the metabolism of ethanol.

Retinoid compounds are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

Methadone

In a pharmacokinetic study, co-administration of 600 mg abacavir twice daily with methadone showed a 35 % reduction in abacavir C_{max} and a 1-hour delay in T_{max}, but the AUC was unchanged.

The changes in abacavir pharmacokinetics are not considered clinically relevant.

In this study, abacavir increased the mean methadone systemic clearance by 22 %.

The induction of metabolising enzymes cannot therefore be excluded.

Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms indicating under dosing, as occasionally methadone re-titration may be required.

Interactions relevant to lamivudine

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

The possibility of interactions with other medicines administered concurrently with DUMIVA DISPERSIBLE TABLETS should be considered, particularly when the main route of elimination is active renal secretion, especially via the cationic transport system e.g. trimethoprim. Other medicines (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine.

The nucleoside analogues (e.g. zidovudine and didanosine) are not metabolised by this mechanism and are unlikely to interact with lamivudine.

Trimethoprim/sulfamethoxazole

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component.

However, unless the patient has renal impairment, no dose adjustment of lamivudine is necessary.

The pharmacokinetics of trimethoprim or sulfamethoxazole are not affected.

When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically.

Co-administration of DUMIVA DISPERSIBLE TABLETS with high doses of co-trimoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis should be avoided.

Ganciclovir or foscarnet

Co-administration of lamivudine with intravenous ganciclovir or foscarnet is not recommended until further information is available.

Zalcitabine

Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used together.

DUMIVA DISPERSIBLE TABLETS are therefore not recommended to be used in combination with zalcitabine.

Medicines by therapeutic area	**Interaction: Geometric mean change (%) (possible**	**Recommendation concerning co-administration**

	mechanism)	
ANTI-INFECTIVE PRODUCTS		
Trimethoprim/ sulfamethoxazole (cotrimoxazole)/ abacavir	Interaction not studied.	No DUMIVA DISPERSIBLE TABLETS dosage adjustment necessary, unless patient has renal impairment.
Trimethoprim/ sulfamethoxazole (co-trimoxazole)/ lamivudine (160 mg/800 mg once daily for 5 days/ 300 mg single dose)	Lamivudine: AUC ↑40 % Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition).	When concomitant administration with 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.
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.
OPIOIDS		

Methadone/ Abacavir (40 to 90 mg once daily for 14 days/ 600 mg single dose, then 600 mg twice daily for 14 days)	Abacavir: AUC ↔ C_{max} ↓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 medicine interaction studies.	Interaction not studied.	
ANTIVIRALS		
Ribavirin/ abacavir	Interaction not studied. Though evidence is conflicting, co-administration of abacavir and ribavirin has been associated with a lower response rate to ribavirin-containing hepatitis C treatment.	If possible, abacavir should be substituted by another NRTI (e.g. tenofovir) when co-treating with ribavirin.
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	Insufficient data to recommend dosage adjustment.

	AUC. The clinical relevance of this is unknown.	
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.
Didanosine/ abacavir Didanosine/ lamivudine Zidovudine/ abacavir	Interaction not studied.	No dose adjustment necessary.
Zidovudine/ lamivudine Zidovudine 300 mg single dose/ lamivudine 150 mg single dose	Lamivudine: AUC ↔ Zidovudine: AUC ↔	
Emtricitabine/ lamivudine		Due to similarities, DUMIVA DISPERSIBLE TABLETS should not be administered concomitantly with other cytidine analogues, such as emtricitabine.
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 concentration versus time curve; C_{max} = maximum observed concentration; CL/F = apparent oral clearance.

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

DUMIVA DISPERSIBLE TABLETS is not recommended during pregnancy (see section 4.3).

The safety of abacavir and lamivudine in human pregnancy has not been established.

Fertility

Studies with abacavir and lamivudine in animals have shown reproductive toxicity.

Breastfeeding

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

Lamivudine is excreted in human milk at similar concentrations to those found in serum.

It is expected that abacavir will also be secreted into human milk, although this has not been confirmed.

It is therefore recommended that mothers do not breastfeed their babies while receiving treatment with DUMIVA DISPERSIBLE TABLETS.

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.

The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipidaemia).

These reactions are often transitory.

Some late-onset neurological disorders have been reported (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.

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 should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

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, as contained in DUMIVA DISPERSIBLE TABLETS, although these reactions may occur at any time during therapy. Close medical supervision is necessary during the first two months, with consultations every two weeks.

It is likely that intermittent therapy may increase the risk of developing sensitisation and therefore occurrence of clinically significant hypersensitivity reactions. Consequently, patients should be advised of the importance of taking DUMIVA DISPERSIBLE TABLETS regularly.

Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue DUMIVA DISPERSIBLE TABLETS and must never be rechallenged with DUMIVA DISPERSIBLE TABLETS, or any other medicine containing abacavir.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, abacavir, as in DUMIVA DISPERSIBLE TABLETS, 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 medicines).

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting abacavir, as in DUMIVA DISPERSIBLE TABLETS, 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 skin rash. 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. In both cases, if a decision is made to restart abacavir, as in DUMIVA DISPERSIBLE TABLETS, this must be done in a setting where medical assistance is readily available.

Each patient must be warned about this hypersensitivity reaction to abacavir, as in DUMIVA DISPERSIBLE TABLETS.

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 DUMIVA DISPERSIBLE TABLETS has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart a medicine containing abacavir, this must be done in a setting where medical assistance is readily available.

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 medicines containing abacavir, as in DUMIVA DISPERSIBLE TABLETS, 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.

Tabulated list of adverse reactions

Body system	Abacavir	Lamivudine
Blood and lymphatic systems disorders		**Less frequent:** Neutropenia and anaemia (both occasionally severe),

		thrombocytopenia, pure red cell aplasia.
Immune system disorders	**Frequent:** Hypersensitivity.	
Metabolism and nutrition disorders	**Frequent:** Anorexia, hyperlactataemia. **Less frequent:** Lactic acidosis, redistribution/ accumulation of body fat.	**Frequent:** Hyperlactataemia. **Less frequent:** Lactic acidosis, redistribution/ accumulation of body fat.
Nervous system disorders	**Frequent:** Headache.	**Frequent:** Headache, insomnia. **Less frequent:** Peripheral neuropathy or paraesthesia.
Respiratory, thoracic and mediastinal disorders		**Frequent:** Cough, nasal symptoms.
Gastrointestinal disorders	**Frequent:** Nausea, vomiting, diarrhoea. **Less frequent:** Pancreatitis.	**Frequent:** Nausea, vomiting, abdominal pain or cramps, diarrhoea. **Less frequent:** Rises in serum amylase, pancreatitis.
Hepatobiliary disorders		**Less frequent:** Transient rises in liver enzymes (AST, ALT), hepatitis.
Skin and subcutaneous tissue disorders	**Frequent:** Rash (without systemic symptoms).	**Frequent:** Rash, alopecia.

	Less frequent: Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.	
Musculoskeletal and connective tissue disorders		**Frequent:** Arthralgia, muscle disorders. **Less frequent:** Rhabdomyolysis.
General disorders and administration site conditions	**Frequent:** Fever, lethargy, fatigue.	**Frequent:** Fatigue, malaise, fever.

Description of selected adverse reactions

In clinical studies approximately 5 % of subjects receiving abacavir developed hypersensitivity reactions.

Some hypersensitivity reactions were life-threatening and resulted in fatal outcome despite taking precautions.

This reaction is characterised by the appearance of symptoms indicating multi- organ/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 or fever.

The signs and symptoms of this hypersensitivity reaction are listed below.

Those reported in at least of 10 % of patients with hypersensitivity reactions are in bold text:

Skin and subcutaneous tissue disorders	**Rash** (usually maculopapular or urticarial).
Gastrointestinal disorders	**Nausea, vomiting, diarrhoea, abdominal pain**, mouth ulceration.
Respiratory, thoracic and mediastinal disorders	**Dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure.
General disorders and	**Fever, lethargy, malaise**, oedema, lymphadenopathy, hypotension,

administrative site conditions	conjunctivitis, anaphylaxis.
Nervous system disorders	**Headache**, paraesthesia.
Blood and the lymphatic system disorders	**Lymphopenia.**
Hepatobiliary disorders	**Elevated liver function tests,** hepatitis, hepatic failure.
Musculoskeletal, connective tissue and bone disorders	**Myalgia, rarely myolysis, arthralgia, elevated creatine phosphokinase.**
Renal and urinary disorders	**Elevated creatinine, renal failure.**

Restarting abacavir, as in DUMIVA DISPERSIBLE TABLETS, 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. 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).

For details of clinical management in the event of a suspected abacavir HSR see section 1 NAME OF MEDICINE – Boxed warning.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms and signs

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

No specific symptoms or signs have been identified following acute overdose with abacavir or lamivudine, apart from those listed as side effects.

Treatment

Treatment should be symptomatic and supportive. 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

PHARMACOLOGICAL CLASSIFICATION:

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC code: J05AR02

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs) and are potent selective inhibitors of HIV-1 and HIV-2.

All two medicines are metabolised sequentially by intracellular kinases to the respective 5′-triphosphate (TP).

Lamivudine-TP, 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, lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture.

Abacavir shows synergy *in vitro* in combination with amprenavir, nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, stavudine and lamivudine.

In vitro resistance: HIV-1 resistance to lamivudine involves the development of a M184I or, more commonly, M184V amino acid change close to the active site of the viral RT.

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the RT codon region (codons M184V, K65R, L74V and Y115F).

Viral resistance to abacavir develops relatively slowly *in vitro*, requiring multiple mutations for a clinically

relevant increase in EC50 over wild-type virus.

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

***In vivo* resistance (therapy experienced patients)**

The M184V or M184I variants arise in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy and confer high-level resistance to lamivudine.

Clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors.

Phenotypic resistance and cross-resistance

Zidovudine, didanosine, stavudine and tenofovir maintain their antiretroviral activities against such HIV-1 variants.

The presence of M184V with K65R does give rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine.

The presence of M184V with Y115F gives rise to cross-resistance between abacavir and lamivudine.

Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

Cross-resistance between abacavir or lamivudine and antiretrovirals from other classes e.g. protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) is unlikely.

5.2 Pharmacokinetic properties

There is no clinically significant food effect observed between administrations of abacavir/lamivudine (FDC) in the fasted or fed state.

These results indicate that FDC can be taken with or without food. The pharmacokinetic properties of lamivudine and abacavir are described below.

Absorption

Abacavir and lamivudine are well absorbed from the gastrointestinal tract following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is about 83 % and 80 – 85 % respectively.

The mean time to maximal serum concentrations (T_{max}) is about 1,5 hours and 1,0 hour for abacavir and lamivudine, respectively.

Following a single dose of 600 mg of abacavir, the mean (CV) C_{max} is 4,26 µg/mL (28 %) and the mean (CV) AUC is 11,95 µg.h/mL (21 %).

Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days, the mean (CV) steady-state C_{max} is 2,04 µg/mL (26 %) and the mean (CV) AUC24 is 8,87 µg.h/mL (21 %).

Distribution

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 medicines 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 CSF concentrations are 9-fold greater than the IC50 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 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.

Special populations

Hepatically impaired

There are no data available on the use of DUMIVA DISPERSIBLE 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 half-life of abacavir.

Dosage reduction of abacavir is likely to be required in patients with mild hepatic impairment.

The separate preparations of abacavir should therefore be used to treat these patients.

The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment.

Plasma concentrations of abacavir are expected to be variable and substantially increased in these patients.

DUMIVA DISPERSIBLE TABLETS is therefore contraindicated in patients with moderate to severe hepatic impairment.

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

Renally impaired

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.

Dose reduction is required for patients with creatinine clearance of < 50 mL/min therefore the separate preparation of lamivudine should be used to treat these patients.

Elderly

No pharmacokinetic data are available in patients over 65 years of age. This medicine is not indicated for use in the elderly.

5.3 Preclinical safety data

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

Mutagenicity and carcinogenicity

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but 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 tested concentrations.

The carcinogenic potential of a combination of abacavir and lamivudine has not been tested. In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential.

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and in the liver, urinary bladder, lymph nodes and the subcutis of females.

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

Repeat-dose toxicity

In toxicology studies abacavir was shown to increase liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, autoinduction of abacavir metabolism or induction of the metabolism of other medicines hepatically metabolised has not been observed in man.

Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for two years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

Reproductive toxicology

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

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

Abacavir demonstrated toxicity to the developing embryo and foetus in rats, but not in rabbits. These

findings included decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and still births. No conclusion can be drawn with regard to the teratogenic potential of abacavir because of this embryo-foetal toxicity. A fertility study in rats has shown that abacavir and lamivudine had no effect on male or female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients of DUMIVA DISPERSIBLE TABLETS are: Croscarmellose sodium, magnesium stearate, microcrystalline cellulose, strawberry flavour (artificial flavours, benzyl alcohol, maltodextrin, propylene glycol, triethyl citrate).

Contains aspartame.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original container.

Do not remove from carton until required for use.

Keep container tightly closed.

6.5 Nature and contents of container

DUMIVA DISPERSIBLE TABLETS are presented in the following: High-density polyethylene (HDPE) bottle pack (marketable pack) comprising of a white opaque HDPE bottle with absorbent cotton and white opaque polypropylene (PP) screw cap with a package insert in an outer carton. Pack size of 28’s, 30’s and 60’s.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Johannesburg, 1609

8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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