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SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

DUMIVA (Film-coated Tablet)

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 WARNINGS).

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, screening for carriage of the HLA-B*5701 allele should be performed. DUMIVA 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, 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 and not rechallenge with DUMIVA 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.

• Clinical Management

Hypersensitivity reaction symptoms usually appear within the first six weeks of initiation of treatment with DUMIVA, 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, with consultation every two weeks.

Patients who are diagnosed with a hypersensitivity reaction whilst on therapy MUST discontinue the fixed-dose combination of DUMIVA tablets immediately.

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

Restarting DUMIVA, 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 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 medicinal products).

Special care is needed for those patients simultaneously starting treatment with the fixed-dose combination of DUMIVA tablets and other medicinal products 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.

• Management after an interruption of the fixed-dose combination of DUMIVA tablets therapy.

If therapy with the fixed-dose combination of DUMIVA 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 or any other medicinal product 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.

- **Essential patient information.**

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 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 tablets or any other medicinal product 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 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 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 tablets regularly.**
- **Each patient should be reminded to read the Patient Information Leaflet included in the fixed-dose combination of DUMIVA tablets package.**
- **They should be reminded of the importance of removing the Alert Card included in the package and keeping it with them at all times.**

COMPOSITION:

DUMIVA constitutes abacavir (as sulfate) and lamivudine in one film-coated tablet.

Each film-coated tablet contains:

Abacavir sulfate equivalent to abacavir 600 mg

Lamivudine 300 mg

Sugar free

List of excipients:

Microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, sodium starch glycolate, Opadry yellow.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Mechanism of action:

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs) and are potent selective inhibitors of HIV-1 and HIV-2. All two medicinal products 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 EC_{50} 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.

Pharmacokinetics:

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 gastro-intestinal tract following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is about 83 % and 80 - 85 % respectively. The mean time to maximal serum concentrations (t_{max}) is about 1,5 hours and 1,0 hours 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$_{\infty}$ is 11,95 µg.h/ml (21 %). Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days, the mean (CV) steady-state C_{max} is 2,04 µg/ml (26 %) and the mean (CV) AUC_{24} is 8,87 µg.h/ml (21 %).

Distribution:

Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0,8 and 1,3 l/kg respectively. Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~ 49 %) to human plasma proteins at therapeutic concentrations. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range

and displays limited plasma protein binding *in vitro* (< 36 %). This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement.

Data show that abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44 %. The observed values of the peak CSF 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 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** 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** is therefore contra-indicated 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.

INDICATIONS:

DUMIVA is a fixed-dose combination of two nucleoside analogues (abacavir and lamivudine). It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age.

CONTRA-INDICATIONS:

DUMIVA is contra-indicated in patients:

- with known hypersensitivity to abacavir, lamivudine, or to any of the excipients (for abacavir hypersensitivity, see **WARNINGS** and **Special Precautions** and **SIDE-EFFECTS AND SPECIAL PRECAUTIONS**)
- with abnormally low neutrophil counts (< 0,75 x 109/l) (see **WARNINGS** and **Special Precautions**)
- with abnormally low haemoglobin levels (< 7,5 g/dl or 4,65 mmol/l) (see **WARNINGS** and **Special Precautions)**
- with severe hepatic impairment
- with severe renal impairment
- who are receiving treatment with emtricitabine

WARNINGS:

Patients who develop a hypersensitivity reaction must discontinue DUMIVA and MUST not be re-challenged with DUMIVA (see SIDE-EFFECTS AND SPECIAL PRECAUTIONS).

Hypersensitivity reaction:

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

Hypersensitivity to abacavir (see **SIDE-EFFECTS**):

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 and MUST NOT be rechallenged with DUMIVA or any other product containing abacavir (see SIDE-EFFECTS AND SPECIAL PRECAUTIONS**).

Lactic acidosis/severe hepatomegaly with steatosis:

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** can result in potentially fatal lactic acidosis. Symptomatic hyperlactataemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase. In patients with suspicious symptoms of biochemistry, measure the venous lactate level (normal < 2 mmol/l) and respond as follows:

- Lactate 2-5 mmol/l: monitor regularly and be alert for clinical signs
- Lactate 5-10 mmol/l without symptoms, monitor closely
- Lactate 5-10 mmol/l with symptoms: STOP all therapy. Exclude other causes e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma
- Lactate > 10 mmol/l: STOP all therapy (80 % mortality in case studies)

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. **The above lactate values may not be applicable to paediatric patients.** Lactic acidosis and severe

hepatomegaly with steatosis, including fatal cases, have been reported with the use of **DUMIVA** alone or in combination.

Caution should be exercised when administering **DUMIVA** to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors of liver disease and hepatic steatosis (including certain medicinal products 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.

Myocardial infarction:

Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall, the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing **DUMIVA**, action should be taken to try to minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia).

Lipodystrophy:

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. 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. Clinical examination should include evaluation for physical signs of fat redistribution. 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.

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:

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.

The safety and efficacy of **DUMIVA** has not been established in patients with significant underlying liver disorders. **DUMIVA** is contra-indicated in patients with severe hepatic impairment.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

If **DUMIVA** 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).

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.

Caution is advised when used in patients with hepatitis B.

INTERACTIONS:

DUMIVA contains abacavir and lamivudine therefore any interactions identified for these individually are relevant to **DUMIVA**. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine.

Abacavir and lamivudine are not significantly metabolised by cytochrome P_{450} enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P_{450} enzymes. The

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

Interactions relevant to abacavir

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

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.

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 medicinal products administered concurrently with **DUMIVA** should be considered, particularly when the main route of elimination is active renal secretion, especially via the cationic transport system e.g., trimethoprim. Other medicinal products (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.

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** with high doses of co-trimoxazole for the treatment of

Pneumocystis jerovicii pneumonia (PCP) and toxoplasmosis should be avoided.

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 medicinal products are used together. **DUMIVA** is therefore not recommended to be used in combination with zalcitabine.

PREGNANCY AND LACTATION:

DUMIVA is not recommended during pregnancy. The safety of abacavir and lamivudine in human pregnancy has not been established. Studies with abacavir and lamivudine in animals have shown reproductive toxicity.

It is recommended that HIV-infected women do not breast-feed 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 breast-feed their babies while receiving treatment with **DUMIVA.**

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.

DOSAGE AND DIRECTIONS FOR USE:

Patients should be stabilised on individual medicines before being switched over to

DUMIVA. Therapy should be initiated by a medical practitioner experienced in the management of HIV infection. **DUMIVA** should not be administered to adults or adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose reduced.

DUMIVA can be taken with or without food.

Adults and adolescents: The recommended dose of **DUMIVA** in adults and adolescents is one tablet once daily.

Special populations:

DUMIVA 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 medicinal products.

Children:

DUMIVA is not recommended for treatment of children as the necessary dose adjustment cannot be made. For these patients other fixed dose formulations are available.

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** 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** the separate preparations should be used when judged necessary. **DUMIVA** must not be used in patients with moderate and severe hepatic impairment.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

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	**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**

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 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 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.

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

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).

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, as in DUMIVA, this must be done in a setting where medical assistance is readily available.

Each patient must be warned about this hypersensitivity reaction to abacavir.

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** 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, 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 medicinal products containing abacavir, as in **DUMIVA,** 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.

Body system	**Abacavir**	**Lamivudine**
Blood and lymphatic systems		*Less frequent:* neutropenia and anaemia (both

disorders		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) *Less frequent:* erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	*Frequent*: rash, alopecia
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

Special Precautions:

Before initiating treatment with **DUMIVA**, 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** in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see “Management after an interruption of **DUMIVA** therapy”). **DUMIVA** 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.

Severe hepatomegaly with steatosis:

Particular caution should be exercised when administering **DUMIVA** 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** 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 Reactivation Syndrome:

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jerovicii* pneumonia. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary.

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

Lipodystrophy:

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Opportunistic infections:

Patients should be advised that **DUMIVA** or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases.

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.

Transmission of HIV:

Patients should be advised that current antiretroviral therapy, including **DUMIVA**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

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

*Ability to drive and use machinery***:**

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

If overdose occurs the patient should be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

IDENTIFICATION:

Yellow coloured, biconvex, film coated tablet, debossed with "M157" on one side and plain on the other side.

PRESENTATION:

DUMIVA is presented in the following:

High Density Polyethylene (HDPE) bottle pack (marketable pack) comprising of a round wide mouth white HDPE bottle with white opaque polypropylene (PP) screw cap with aluminium induction sealing wad with a package insert in an outer carton. Pack size of 28's or 30.

High Density Polyethylene (HDPE) bottle pack (marketable pack) comprising of a blue wide mouth blue opaque HDPE bottle with blue opaque polypropylene screw cap with aluminium induction sealing liner wad with a package insert in an outer carton. Pack size of 28's or 30.

PVC/Aclar blister pack (marketable pack) comprises of clear, transparent, PVC film coated with Aclar on one side (i.e. PVC/Aclar) and hard tempered aluminium foil (coated with VMCH heat seal lacquer) on other side with a package insert in an outer carton. Pack size of 28's or 30.

STORAGE INSTRUCTIONS:

Store at or below 30 ˚C. Protect from light.

Store in the original container. Keep the blisters in the outer carton until required for use.

Keep the container tightly closed.

KEEP OUT OF REACH AND SIGHT OF CHILDREN

REGISTRATION NUMBER:

46/20.2.8/0012

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

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