PACKAGE INSERT - Clean

SCHEDULING STATUS:

Schedule 4

PROPRIETARY NAME (AND DOSAGE FORM):

KAVIMUN (film-coated tablets)

COMPOSITION:

Each **KAVIMUN** film-coated tablet contains:

Abacavir sulfate equivalent to abacavir	300 mg. Sugar free

List of Excipients: cellulose microcrystalline, silica colloidal anhydrous, magnesium stearate, sodium starch glycolate, film-coat {[hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide yellow, iron oxide red}

WARNING:

Hypersensitivity to abacavir:

In clinical studies, conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction. In some cases, this has proven fatal.

Risk factors:

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. In one study, use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele, reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7,8 % to 3,4 % and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2,7 % to 0,0 %. Based on this study, it is estimated that 48 % to 61 % of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0 % to 4 % of patients who do not have the HLA-B*5701 allele. It is recommended that any HIV-infected patient without prior exposure to abacavir, be screened for HLA-B*5701 allele.

Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.

Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended and should be considered only under exceptional circumstances where the potential benefit outweighs the risk, and with close medical supervision.

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

Clinical description:

The hypersensitivity reaction is characterised by the appearance of symptoms indicating multi-organ involvement. The majority of patients have fever and/or rash as part of the syndrome. Some of the other symptoms of hypersensitivity may include fatigue, malaise, gastrointestinal symptoms such as nausea, vomiting, diarrhoea, or abdominal pain, and respiratory signs and symptoms such as dyspnoea, sore throat, cough and abdominal chest x-ray findings (predominantly infiltrates, which can be localised). The symptoms of this hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks of therapy. The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Clinical management:

Regardless of their HLA-B*5701 allele status, any patient developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice.

Management after an interruption of KAVIMUN tablets therapy:

Regardless of a patient's HLA-B*5701 status, if therapy with **KAVIMUN** 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, **KAVIMUN** tablets or any other medicinal product containing abacavir must not be restarted.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting **KAVIMUN** 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 **KAVIMUN** tablets. 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 (i.e. patients previously considered to be abacavir tolerant). In both cases, if a decision is made to restart **KAVIMUN** tablets this must be done in a setting where medical assistance is readily available.

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

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 **KAVIMUN** that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.

- patients must also be informed that a HLA-B*5701 negative patient can also experience an abacavir hypersensitivity reaction. **Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT THEIR DOCTOR IMMEDIATELY.**

- patients who are hypersensitive to abacavir should be reminded that they must never take **KAVIMUN** tablets or any other medicinal product containing abacavir again, regardless of their HLA-B*5701 status.

- in order to avoid restarting **KAVIMUN** tablets, patients who have experienced a hypersensitivity reaction should be asked to return the remaining **KAVIMUN** tablets

- patients who have stopped **KAVIMUN** tablets for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.

- each patient should be reminded to read the Patient Information Leaflet included in the **KAVIMUN** pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Abacavir is a nucleoside analogue reverse transcriptase inhibitor (NRTI). It is a potent selective inhibitor of HIV-1 and HIV-2. Abacavir is metabolised intracellularly to the active moiety, carbovir 5'- triphosphate (TP). *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event which results in chain termination and interruption of the viral replication cycle. Abacavir shows synergy *in vitro* in combination with nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, lamivudine and stavudine.

***In vitro resistance*:**

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

Pharmacokinetic properties:

Absorption:

Abacavir is well absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83 %. Following oral administration, the mean time (t_{max}) to maximal serum concentrations of abacavir is about 1,5 hours for the tablet formulation and about 1,0 hour for the solution formulation.

At therapeutic dosages a dosage of 300 mg twice daily, the mean (CV) steady state C_{max} and C_{min} of abacavir are approximately 3,00 µg/ml (30 %) and 0,01 µg/ml (99 %), respectively. The mean (CV) AUC over a dosing interval of 12 hours was 6,02 µg.h/ml (29 %), equivalent to a daily AUC of approximately 12,0 µg.h/ml. The C_{max} value for the oral solution is slightly higher than the tablet. After a 600 mg abacavir tablet dose, the mean (CV) abacavir C_{max} was approximately 4,26 µg/ml (28 %) and the mean AUC was 11,95 µg.h/ml (21 %).

Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore **KAVIMUN** tablets can be taken with or without food.

Distribution*:*

Following intravenous administration, the apparent volume of distribution was about 0,8 l/kg, indicating that abacavir penetrates freely into body tissues.

Studies in HIV infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44 %. The observed values of the peak concentrations are 9 fold greater than the IC_{50} of abacavir of 0,08 µg/ml or 0,26 µM when abacavir is given at 600 mg twice daily**.**

Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~ 49 %) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement.

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. The metabolites are excreted in the urine.

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.

Special populations:

Hepatically impaired:

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

[1,32; 2,70] in the abacavir AUC, and 1,58 [1,22; 2,04] fold in the elimination half-life. No recommendation on dosage reduction is possible in patients with mild hepatic impairment due to the substantial variability of abacavir exposure.

Renally impaired:

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. Therefore no dosage reduction is required in patients with renal impairment. Based on limited experience Abacavir tablets should be avoided in patients with end-stage renal disease.

Children:

According to clinical trials performed in children abacavir and well absorbed from an oral solution administered to children. The overall pharmacokinetic parameters in children are comparable to adults, with greater variability in plasma concentrations. The recommended dose for children from three months to 12 years is 8 mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve therapeutic concentrations equivalent to 300 mg twice daily in adults.

There are insufficient safety data to recommend the use of **KAVIMUN** tablets in infants less than three months old. The limited data available indicate that a dose of 2 mg/kg in neonates less than 30 days old provides similar or greater AUCs, compared to the 8 mg/kg dose administered to older children.

This formulation (300 mg tablets) is not suitable for small children.

Elderly:

The pharmacokinetics of abacavir has not been studied in patients over 65 years of age.

INDICATIONS:

KAVIMUN tablets are indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) infection.

The demonstration of the benefit of **KAVIMUN** tablets is mainly based on results of studies performed with a twice daily regimen, in treatment-naïve adult patients on combination therapy.

CONTRA-INDICATIONS:

KAVIMUN is contra-indicated:

- In patients with known hypersensitivity to **KAVIMUN** or any ingredient of the formulation. Never restart **KAVIMUN** or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status

- (*see* **WARNINGS; DOSAGE AND DIRECTIONS FOR USE; SIDE-EFFECTS and SPECIAL PRECAUTIONS**)

- In patients with moderate or severe liver function impairment

- During pregnancy and lactation

WARNINGS:

Hypersensitivity reaction:

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

Hypersensitivity to abacavir:

In clinical studies, approximately 5 % of subjects receiving abacavir developed a hypersensitive reaction, which in some cases has proven fatal. Hypersensitivity is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. **Patients who develop a hypersensitivity reaction must discontinue KAVIMUN and MUST NOT be rechallenged with KAVIMUN or any other product containing abacavir (see SIDE-EFFECTS AND SPECIAL PRECAUTIONS**).

Lactic acidosis: Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues, such as **KAVIMUN**. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with **KAVIMUN** should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels (see **Special Precautions**).

Caution should be exercised when administering **KAVIMUN** to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for 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.

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 (see **Special Precautions**).

Liver disease:

The safety and efficacy of **KAVIMUN** has not been established in patients with significant underlying liver disorders. **KAVIMUN** 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 events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

A pharmacokinetic study has been performed in patients with mild hepatic impairment. However, a definitive recommendation on dose reduction is not possible due to substantial variability of abacavir exposure in this patient population. The clinical safety data available with abacavir in hepatically impaired patients is very limited. Due to the potential increases in exposure (AUC) in some patients, close monitoring is required. No data are available in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to substantially increase in these patients. Therefore, the use of **KAVIMUN** in patients with moderate hepatic impairment is not recommended.

For patients with severe hepatic impairment, **KAVIMUN** is contra-indicated.

Renal disease:

KAVIMUN should not be administered to patients with end-stage renal disease.

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 while taking **KAVIMUN.**

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 mycobacterium infections, and *Pneumocystis jerovicii (carinii)* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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 **KAVIMUN** tablets, action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

INTERACTIONS:

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for P450 mediated interactions with other medicinal products involving abacavir is low. P450 does not play a major role in the metabolism of abacavir, and abacavir does not inhibit metabolism mediated by CYP 3A4. Abacavir has also been shown *in vitro* not to inhibit CYP 3A4, CYP2C9 or CYP2D6 enzymes at clinically relevant concentrations. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for interactions with antiretroviral protease inhibitors and other medicinal products metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

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 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.

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 one 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 substance metabolising enzymes cannot therefore be excluded. Patients being treated with methadone and **KAVIMUN** should be monitored for evidence of withdrawal symptoms indicating under dosing, as occasionally methadone re-titration may be required.

Retinoids:

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

PREGNANCY AND LACTATION:

Pregnancy:

KAVIMUN is not recommended during pregnancy. The safe use of **KAVIMUN** in human pregnancy has not been established. Placental transfer of abacavir and/or its related metabolites has been shown to occur in animals. Toxicity to the developing embryo and

foetus occurred in rats, but not in rabbits. The teratogenic potential of abacavir could not be established from studies in animals.

Lactation:

Abacavir and its metabolites are secreted into the milk of lactating rats. It is expected that these will also be secreted into human milk, although this has not been confirmed. There are no data available on the safety of abacavir when administered to babies less than three months old. It is therefore recommended that mothers do not breast-feed their babies while receiving treatment with **KAVIMUN**. Additionally, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

DOSAGE AND DIRECTIONS FOR USE:

KAVIMUN tablets should be prescribed by medical practitioners experienced in the management of HIV infection.

KAVIMUN tablets can be taken with or without food.

Adults and adolescents over 12 years:

The recommended dose of **KAVIMUN** is 600 mg daily. This may be administered as either 300 mg (one tablet) twice daily or 600 mg (two tablets) once daily.

Patients changing to the once daily regimen should take 300 mg twice a day and switch to 600 mg once a day the following morning. Where an evening once daily regimen is preferred, 300 mg of **KAVIMUN** should be taken on the first morning only, followed by 600 mg in the evening. When changing back to a twice daily regimen, patients should complete the day's treatment and start 300 mg twice a day the following morning.

Renal impairment:

No dosage adjustment of **KAVIMUN** is necessary in patients with renal dysfunction. However, **KAVIMUN** should be avoided in patients with end-stage renal disease.

Hepatic impairment:

Abacavir is primarily metabolised by the liver. No dose recommendation can be made in patients with mild hepatic impairment. No data are available in patients with moderate hepatic impairment, therefore the use of **KAVIMUN** is not recommended.

In patients with mild and moderate hepatic impairment close monitoring is required, and if feasible, monitoring of abacavir plasma levels is recommended. **KAVIMUN** is contra-indicated in patients with severe hepatic impairment.

Elderly:

No pharmacokinetic data is currently available in patients over 65 years of age.

Before initiating treatment with **KAVIMUN**, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Screening is also recommended prior to re-initiation of **KAVIMUN** in patients of unknown

HLA-B*5701 status who have previously tolerated **KAVIMUN** (see Management after an interruption of **KAVIMUN** therapy). **KAVIMUN** 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.

Refer block Warning at the beginning of this package insert.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Hypersensitivity:

In a clinical study, 5 % of subjects with a negative HLA-B*5701 status receiving abacavir developed a hypersensitivity reaction. In clinical studies with abacavir 600 mg once daily the reported rate of hypersensitivity remained within the range recorded for abacavir 300 mg twice daily.

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

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.

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

have been identified either from clinical studies or post marketing surveillance. Those reported **in at least 10 % of patients** with a hypersensitivity reaction are in bold text.	
Skin	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract	**Nausea, vomiting, diarrhoea, abdominal pain** , mouth ulceration
Respiratory tract	**Dyspnoea, cough** , sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous	**Fever, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry	**Headache** , paraesthesia
Haematological	Lymphopenia
Liver/pancreas	**Elevated liver function tests,** hepatitis, hepatic failure
Musculoskeletal	**Myalgia** , rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology	Elevated creatinine, renal failure

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

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. This delay in diagnosis of hypersensitivity has resulted in abacavir being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, although these reactions may occur at any time during therapy. Close medical supervision is necessary during the first two months, with consultations every two weeks.

Many of those listed below occur frequently (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 a hypersensitivity reaction. If abacavir 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.

Less frequently cases of erythema multiforme, Stevens Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicinal products containing abacavir should be permanently discontinued.

Metabolism and nutrition disorders:

Frequent: Anorexia

Frequency not known: Redistribution/accumulation of body fat, hypertriglyceridaemia, hyperglycaemia, hyperlactataemia

Nervous system disorders:

Frequent: Headache

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea

Less frequent: Pancreatitis

Hepatobiliary disorders:

Frequency not known: Hepatitis, lactic acidosis, severe hepatomegaly with steatosis

Skin and subcutaneous disorders:

Frequent: Skin rash (without systemic symptoms)

Less frequent: Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome

General disorders and administration site conditions:

Frequent: Fever, lethargy, fatigue

Special Precautions:

Lactic acidosis:

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

Use of **KAVIMUN** can result in potentially fatal lactic acidosis.

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)

The above lactate values may not be applicable to paediatric patients.
Caution should be exercised when administering **KAVIMUN** to patients with known risk factors of liver disease (see **WARNINGS).**
Treatment with **KAVIMUN** should be suspended in any patient who develops clinical or laboratory findings of lactic acidosis or hepatotoxicity.

Hypersensitivity:

Risk factors that may predict the occurrence or severity of hypersensitivity to abacavir have not been identified. However, 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 abacavir regularly.

Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction was usually more severe than on initial presentation, and may include life-threatening hypotension and death. **Regardless of their HLA10 B*5701 status, patients who develop this hypersensitivity reaction must discontinue abacavir and must never be rechallenged with abacavir or any other medicinal product containing abacavir.**

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, **KAVIMUN** 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 medications). **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 **KAVIMUN** this must be done in a setting where medical assistance is readily available.

Each patient must be warned about this hypersensitivity reaction to **KAVIMUN**.

Fat redistribution:

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).

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

Immune reactivation syndrome:

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART) an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see **WARNINGS**).

Osteonecrosis:

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see **WARNINGS**).

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Severe Hepatomegaly with Steatosis:

Particular caution should be exercised when administering **KAVIMUN** 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 **KAVIMUN** 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).

Myocardial Infarction:

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimise all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, and smoking) (see **WARNINGS**).

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 events reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events 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 **KAVIMUN**, 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.

Pancreatitis:

Pancreatitis has been reported, but a causal relationship to **KAVIMUN** treatment is uncertain.

Triple nucleoside therapy:

In patients with high viral load (>100,000 copies/ml) the choice of a triple combination with abacavir, lamivudine and zidovudine needs special consideration.

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when **KAVIMUN** was combined with tenofovir disoproxil fumarate and lamivudine as a once daily regimen.

Opportunistic infections:

Patients receiving **KAVIMUN** or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by medical practitioners experienced in the treatment of these associated HIV diseases.

Transmission:

Patients should be advised that current antiretroviral therapy, including **KAVIMUN**, have 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.

Effects on ability to drive and use machines:

No currently available data suggest that **KAVIMUN** affects the ability to drive or operate machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Single doses up to 1200 mg and daily doses up to 1800 mg of **KAVIMUN** tablets have been administered to patients in clinical studies.

The effects of higher doses are not known. If overdose occurs the patient should be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

IDENTIFICATION:

Peach coloured, capsule shaped biconvex film-coated tablet, debossed with “M110” on one side and plain on the other.

PRESENTATION:

KAVIMUN is packed in a white coloured HDPE bottle with white opaque polypropylene (PP) screw cap with induction sealing liner, packaged in a carton or **KAVIMUN** is packed

in a round blue opaque high density polyethylene (HDPE) bottle with blue opaque polypropylene (PP) screw cap with induction sealing liner, packaged in a carton or **KAVIMUN** is packed in a PVC/PVdC blister pack (marketable pack) comprising of a clear, transparent, PVC film coated with PVdC on one side (i.e., PVC/PVdC) and aluminium foil coated with VMCH heat seal lacquer on other side. Blisters are presented in a carton. Pack size of 56's or 60's.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Store in the original container until required for use. Protect from light. Do not use if seal over bottle opening is broken or missing. Keep the container tightly closed.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER:

46/20.2.8/0979

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

Viatris Healthcare (Pty) Ltd.

4 Brewery Street

Isando, Gauteng,

1601

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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