PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE:

VEXABAX 600 mg/300 mg Film-coated tablets

Hypersensitivity to abacavir (see also Section 4.8 Undesirable effects).

Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSR can be life-threatening and may be fatal, when not managed appropriately. The risk for abacavir HSR to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

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 proved 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 the prospective study CNA106030 (PREDICT-1), 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 % (66 of 847) to 3,4 % (27 of 803) ($p < 0,0001$) and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2,7 % (23 of 842) to 0,0 % (0 of 802) ($p < 0,0001$). 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 *(see Special considerations following an interruption of VEXABAX therapy).* Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended. 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 abnormal 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.

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respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal 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 status, any patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed, VEXABAX MUST be discontinued immediately. VEXABAX, or any other medicine containing abacavir, MUST NEVER be restarted following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, VEXABAX should 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). VEXABAX, or any other medicine containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medicine(s). Alert information for the patient about this hypersensitivity reaction is included on the side of the VEXABAX pack.

Special considerations following an interruption of VEXABAX therapy:

Regardless of a patient's HLA-B*5701 status, if therapy with VEXABAX or any abacavir containing product has been discontinued and restarting therapy with VEXABAX is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If a hypersensitivity reaction cannot be ruled out, VEXABAX or any other medicine containing abacavir should not be restarted**. There have been infrequent reports of hypersensitivity reaction following re-introduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart VEXABAX in these patients, this should be done only under direct medical supervision.

Hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to restart VEXABAX, this must be done only if medical care can be accessed readily by the patient or others.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of VEXABAX in patients of unknown HLA-B*5701 status who have previously tolerated VEXABAX. Re-initiation of VEXABAX in such patients who test positive for the HLA B*5701 allele is not recommended.

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 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 HLA-B*5701 negative patients can also experience 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 VEXABAX or any other medicine containing abacavir again, regardless of their HLA-B*5701 status

- in order to avoid restarting VEXABAX, patients who have experienced a hypersensitivity reaction should be asked to return the remaining VEXABAX tablets to the pharmacy - patients who have stopped VEXABAX 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 package leaflet included in the VEXABAX pack. They should be reminded of the importance of keeping the Alert Information included on the side of the pack and keeping it with them at all times.

2. QUALITATIVE AND QUANTITIVE COMPOSITION:

Each film-coated tablet contains abacavir sulphate equivalent to abacavir 600 mg and lamivudine 300 mg. Sugar-free.

3. PHARMACEUTICAL FORM:

Film-coated tablet (tablet).

Orange coloured capsule shaped, film coated tablets, debossed with ‘RF 90’ on one side and break line on other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

VEXABAX is a 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, weighing at least 40 kg.

4.2 Posology and method of administration:

Patients should be stabilised on individual medicines before being switched over to VEXABAX. Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

VEXABAX should not be administered to adults or adolescent patients who weigh less than 40 kg because it is a fixed-dose tablet that cannot be dose reduced. VEXABAX can be taken with or without food. VEXABAX 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.

Adults and adolescents weighing at least 40 kg:

The recommended dose of VEXABAX in adults and adolescents weighing 40 kg or more is one tablet once daily.

Children weighing less than 40 kg:

VEXABAX is not recommended for treatment of children weighing less than 40 kg, as the necessary dose adjustment cannot be made. Medical practitioners should refer to the individual product information for lamivudine and abacavir.

Elderly:

The pharmacokinetics of abacavir and lamivudine have not been studied in patients over 65 years of age. When treating elderly patients, consideration needs to 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 impairment, a dose reduction of lamivudine is required due to decreased clearance. Therefore, VEXABAX is not recommended for use in patients with a creatinine clearance less than 50 ml/min (see section 5.2 Pharmacokinetic properties).

Hepatic impairment: A dose reduction of abacavir may be required for patients with mild hepatic impairment (Child-Pugh grade A). As dose reduction is not possible with VEXABAX, the separate preparation of abacavir should be used when this is judged necessary. VEXABAX is contraindicated in patients with moderate and severe hepatic impairment (see section 5.2 Pharmacokinetic properties).

4.3 Contraindications:

VEXABAX is contraindicated in patients with known hypersensitivity to abacavir or lamivudine, or to any of the excipients. VEXABAX is contraindicated in patients with moderate and severe hepatic impairment.

VEXABAX is contraindicated in children below 12 years of age (weighing less than 40 kg) as the necessary dose adjustment cannot be made.

4.4 Special warnings and precautions for use:

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 VEXABAX.

Hypersensitivity to abacavir (see Section 4.8 Undesirable effects): 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, which in rare cases has proved fatal.

Hypersensitivity is characterised by the appearance of symptoms indicating multiorgan/body-system involvement. **Patients who develop a hypersensitivity reaction must discontinue VEXABAX and MUST NOT be rechallenged with VEXABAX, or any other product containing abacavir** (see section 1 NAME OF MEDICINE - Boxed warning).

Lactic acidosis/severe hepatomegaly with steatosis:

Long-term use of VEXABAX can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Symptomatic hyperlactataemia and lactic acidosis are uncommon. Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea and tachypnoea, 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 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 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).

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 VEXABAX alone or in combination. Caution should be exercised when administering VEXABAX particularly to those with known risk factors for liver disease. Treatment with VEXABAX should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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.

Pancreatitis*:*

Pancreatitis has been observed in some patients receiving VEXABAX. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of VEXABAX until diagnoses of pancreatitis is excluded.

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 blood 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.

Immune Reconstitution Inflammatory Syndrome:

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections 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 ART. Relevant examples are tuberculosis, cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci (P. carinii)* pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease) have also been reported as immune reconstitution syndrome reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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.

Patients co-infected with hepatitis B or C virus:

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for 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 professional information for these medicines. Patients co-infected with HIV and HBV who discontinue VEXABAX 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. Clinical study and marketed use of lamivudine have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If VEXABAX is discontinued in patients coinfected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

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 VEXABAX, action should be taken to minimize 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.

Myocardial Infarction:

In a prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous six months was correlated with an increased risk of myocardial infarction. In a

pooled analysis of reported clinical-trials no excess risk of myocardial infarction was observed with abacavir use.

Opportunistic infections:

Patients receiving VEXABAX or any other anti – retroviral therapy may 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 of infection:

Patients should be advised that current antiretroviral therapy, including VEXABAX, 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.

4.5 Interactions with other medicines and other forms of interaction:

As VEXABAX contains abacavir and lamivudine, any interactions that have been identified with these medicines individually may occur with VEXABAX. 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 medicines metabolised by major P_{450} enzymes. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding and almost complete renal clearance. Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicines administered concurrently should be considered, particularly when the main route of elimination is renal.

Interactions relevant to abacavir:

Ethanol - The metabolism of abacavir is altered by concomitant ethanol intake, resulting in an increase in AUC of abacavir of about 41 %. Given the safety profile of abacavir, 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 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 %. This change is not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.

Interactions relevant to lamivudine:

Trimethoprim - Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg (cotrimoxazole) causes a 40 % increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see 4.2 Posology and method of administration). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of coadministration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis carinii* pneumonia and toxoplasmosis has not been studied.

Zalcitabine - Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicines are used concurrently. VEXABAX is therefore, not recommended to be used in combination with zalcitabine.

Emtricitabine - Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicines are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabline is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these medicines in combination therapy

may be limited. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

The safety of VEXABAX in human pregnancy has not been established.

VEXABAX should not be used during pregnancy and lactation since teratogenicity and/or foetal toxicity cannot be excluded.

Lactation:

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. Therefore, mothers on treatment with VEXABAX should not breastfeed their babies. HIV infected women should not breastfeed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, the local official lactation and treatment guidelines should be followed when considering breastfeeding during antiretroviral therapy.

4.7 Effects on ability to drive and use machines:

There have been no studies to investigate the effect of VEXABAX on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of these medicines. The clinical status of the patient and the adverse event profile of VEXABAX should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects:

VEXABAX contains abacavir and lamivudine, therefore the adverse events associated with these may be expected.

Many of the adverse events listed 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 this hypersensitivity reaction. If VEXABAX has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only under direct medical supervision (see Special considerations following an interruption of VEXABAX therapy in section 1 NAME OF MEDICINE - Boxed warning).

Body System	Abacavir	Lamivudine
Blood and lymphatic systems disorders		**Less frequent:** neutropenia, anaemia, thrombocytopenia, pure red cell aplasia
Immune system disorders	**Frequent:** medicine hypersensitivity	
Metabolism and nutrition disorders	**Frequent:** anorexia **Less Frequent:** hyperlactataemia [1]lactic acidosis	**Less Frequent:** hyperlactataemia [1]lactic acidosis
Nervous system disorders	**Frequent:** headache	**Frequent:** headache **Less Frequent:** paraesthesiae, peripheral neuropathy has been reported although a causal relationship to treatment is uncertain

Gastrointestinal disorders	**Frequent:** nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration **Less frequent:** pancreatitis, but a causal relationship to abacavir is uncertain	**Frequent:** nausea, vomiting, upper abdominal pain, diarrhoea **Less frequent:** rises in serum amylase, pancreatitis, although a causal relationship to lamivudine is uncertain
Hepatobiliary disorders		**Less frequent:** transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	**Frequent:** rash, (without systemic symptoms) **Less frequent:** erythema multiforme, StevensJohnson syndrome and toxic epidermal necrolysis	**Frequent:** rash **Less frequent:** alopecia
Musculoskeletal and connective tissue disorders		**Frequent:** arthralgia, muscle disorders **Less frequent:** muscle rhabdomyolysis
General disorders and administration site conditions	**Frequent:** fever, lethargy, fatigue	**Frequent:** fatigue, malaise, fever

[1] Lactic acidosis (see section 4.4 Special warnings and precautions for use)

Description of Selected Adverse Reactions

Hypersensitivity (see section 1 NAME OF MEDICINE - Boxed warning and section 4.4 Special warnings and precautions for use): Abacavir hypersensitivity reaction (HSR) has been identified as a common adverse reaction with abacavir therapy. 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.

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. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

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 administrative site conditions: **fever, fatigue, malaise,** oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis

Nervous system disorders: **headache,** paraesthesiae

Blood and the lymphatic system disorders: lymphopaenia

Hepato-biliary disorders: **elevated liver function tests,** 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 following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is usually more severe than on initial presentation and may include 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 events:

Reporting suspected adverse events after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reaction Reporting form', found on line under SAHPRA publications, https://www.sahpra.org.za/Publications/index/8

4.9 Overdose:

Symptoms and Signs:

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

Treatment:

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:

Category A, 20.2.8 Antiviral agents.

ATC code: JO5AR02

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

Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective triphosphate (TP) which are the active moieties. Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

The antiviral activity of abacavir in cell culture was not antagonised when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral RT. This variant arises both in vitro and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity in vitro. Studies in vitro indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

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* and *in vivo*, requiring multiple mutations to reach an eight-fold increase in IC_{50} over wild-type virus, which may be a clinically relevant level. Isolates resistant to abacavir might also show reduced sensitivity to lamivudine, zalcitabine, tenofovir, emtricitabine and/or didanosine, but remain sensitive to zidovudine and stavudine.

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

Reduced 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.

Clinical isolates with three or more mutations associated with NRTIs are unlikely to be susceptible to abacavir. Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral medicines. Zidovudine, stavudine, abacavir and tenofovir maintain their antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation.

5.2 Pharmacokinetic properties:

Absorption:

Abacavir and lamivudine are rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is 83 % and 80 to 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 oral dose of 600 mg of abacavir, the mean C_{max} is 4,26 μg/ml and the mean AUC_{∞} is 11,95 μg.h/ml. Following multiple-dose oral administration of lamivudine 300 mg once daily for seven days the mean steady-state C_{max} is 2,04 μg/ml and the mean AUC_{24} is 8,87 μg.h/ml.

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 low plasma protein binding (less than 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 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 to 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 less than 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 unchanged by renal excretion. The likelihood of metabolic interactions with lamivudine is low due to the small extent of hepatic metabolism (less than 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 (greater than 70 %) via the organic cationic transport system.

Special Patient Populations:

Hepatically impaired - 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 to 6). 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. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased.

Dosage reduction of abacavir is likely to be required in patients with mild hepatic impairment. The separate preparation 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. VEXABAX is therefore contraindicated in patients with moderate and severe hepatic impairment. Data obtained for lamivudine in patients with moderate to severe hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction.

Renally impaired - Pharmacokinetic data have been obtained for abacavir and lamivudine 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 less than 50 ml/min, therefore the separate preparation of lamivudine should be used to treat these patients

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Cellulose microcrystalline, magnesium stearate, silica colloidal anhydrous, sodium starch glycollate.

The tablets are film-coated with a coating material containing FD&C yellow/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80 and titanium dioxide.

Sugar free

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

36 months

6.4 Special precautions for storage:

KEEP OUT OF THE REACH OF CHILDREN.

Store at or below 25 °C. Protect from moisture.

6.5 Nature and contents of container:

HDPE Bottle pack comprising of a white opaque HDPE bottle having a white polypropylene child resistant closure (with induction seal liner) or screw closure (with induction seal liner). The bottles contain 28, 30 or 90 film-coated tablets with or without a carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road, Stormill, Ext.1,

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER:

54/20.2.8/0219

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Date of registration: 18 August 2020

10. DATE OF REVISION OF TEXT:

08 April 2024