1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ASPEN ABACAVIR 300 (film-coated tablets)

ZA_ASABACTAB_1706_03

WARNING
Hypersensitivity: **In clinical studies, approximately 4 % of subjects receiving ASPEN ABACAVIR 300 developed a hypersensitivity reaction which may be fatal.**
Description: **This is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. The majority of patients have fever and/or rash as part of the syndrome. The symptoms of this hypersensitivity reaction can occur at any time during treatment with ASPEN ABACAVIR 300, but usually appear within the first 6 weeks of initiation of treatment with ASPEN ABACAVIR 300 (median time to onset 11 days), and most often include fever, gastrointestinal symptoms (nausea, vomiting, diarrhoea and abdominal pain), rash and fatigue or generalised malaise. Other symptoms may include myalgia, arthralgia, oedema, paraesthesia and respiratory symptoms such as dyspnoea, sore throat or cough or pharyngitis.**
The symptoms worsen with continued therapy and can be life-threatening. These symptoms

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usually resolve upon discontinuation of ASPEN ABACAVIR 300.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to ASPEN ABACAVIR 300. Prior to initiating therapy with ASPEN ABACAVIR 300, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated ASPEN ABACAVIR 300. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to ASPEN ABACAVIR 300; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Management: To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, ASPEN ABACAVIR 300 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).

ASPEN ABACAVIR 300 should not be re-started even if a recurrence of symptoms occurs following re-challenge with alternative medication(s).

An Alert Card with information for the patient about recognition of the hypersensitivity reaction is included in the ASPEN ABACAVIR 300 pack and should be dispensed with each new prescription and refill.

Patients who have stopped ASPEN ABACAVIR 300 due to possible adverse reactions or illness should be advised to contact their doctor before restarting. Regardless of HLA-

B*5701 status, permanently discontinue ASPEN ABACAVIR 300 if hypersensitivity cannot be ruled out, even when other diagnoses are possible. ASPEN ABACAVIR 300 or any other medicine containing abacavir should not be restarted because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

There have been infrequent reports of hypersensitivity reaction following re-introduction of ASPEN ABACAVIR 300, where the interruption was preceded by a single key symptom (e.g. rash, fever, malaise/fatigue, gastrointestinal symptoms or respiratory symptoms). Hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction. These hypersensitivity reactions can be serious or fatal. Such reactions can occur within hours. If a decision is made to restart ASPEN ABACAVIR 300, this must be done only if medical care can be assessed readily by the patient or others.

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

- **Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir such as contained in ASPEN ABACAVIR 300 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 ASPEN ABACAVIR 300 or any other medicinal product containing abacavir again.**
- **In order to avoid restarting ASPEN ABACAVIR 300, patients who have experienced a**

hypersensitivity reaction should be asked to return the remaining ASPEN ABACAVIR 300 tablets to the pharmacy.

- **Patients who have stopped ASPEN ABACAVIR 300 for any reason, and particularly due to 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 ASPEN ABACAVIR 300 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 (see WARNINGS AND SPECIAL PRECAUTIONS).**

COMPOSITION

Each ASPEN ABACAVIR 300 tablet contains the equivalent of 300 mg abacavir as abacavir sulphate.

Excipients

Colloidal silicon dioxide, hypromellose, iron oxide yellow (C.I. no. 77492), macrogol, magnesium stearate, microcrystalline cellulose (PH-200), sodium starch glycollate (type A), titanium dioxide (C.I. no. 77891).

Sugar free

CATEGORY AND CLASS

A 20.2.8 Antivirals

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Abacavir is a nucleoside analogue reverse transcriptase inhibitor. It is an antiviral medicine against HIV-1 and HIV-2, including HIV-1 isolates that are resistant to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine. *In vitro* studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event that 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, zalcitabine, lamivudine and stavudine.

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* 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 may also show reduced sensitivity to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. Cross-resistance between abacavir and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is unlikely. Treatment failure following initial therapy with abacavir, lamivudine and zidovudine is mainly associated with the M184V alone, thus maintaining many therapeutic options for a second line regimen.

In antiretroviral naïve patients, abacavir in combination provides effective initial therapy. In therapy experienced patients, limited data show that the addition of ASPEN ABACAVIR 300 to nucleoside reverse transcriptase inhibitors provides additional benefit in reducing viral load, and increasing CD_4 cell count. The degree of benefit will depend on the nature and duration of prior therapy, which may have selected for cross-resistance to abacavir.

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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.

Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore ASPEN ABACAVIR 300 can be taken with or without food.

Distribution

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 %. In a Phase 1 pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300 mg twice a day. The mean concentration of abacavir achieved in the CSF 1,5 hours post dose was 0,14 µg/ml.

In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0,13 µg/ml at 0,5 to 1 hour after dosing, to approximately 0,74 µg/ml after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9 fold greater than the IC_{50} of abacavir of 0,08 µg/ml or 0,26 µM.

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

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 dose 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. 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

Hepatic impairment

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 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. The pharmacokinetics have not been studied in patients with moderate or severe hepatic impairment, therefore abacavir is contraindicated in these patient groups.

Renal impairment

Abacavir is primarily metabolised by the liver with approximately 2 % of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment. However, abacavir is not recommended for patients with end-stage renal disease (see WARNINGS AND SPECIAL PRECAUTIONS).

Children

ASPEN ABACAVIR 300 is a tablet formulation for dosage in adult patients. It is not suitable for children.

Elderly

The pharmacokinetics of abacavir 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, and concomitant disease or other medicine therapy.

INDICATIONS

ASPEN ABACAVIR 300 is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV-1) in infected adults.

CONTRAINDICATIONS

ASPEN ABACAVIR 300 is contraindicated:

- In patients with known hypersensitivity to abacavir or any ingredients of the formulation. Never restart ASPEN ABACAVIR 300 or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status (see SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS),

- In patients with moderate or severe hepatic impairment.
- During pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS

Hypersensitivity reaction (see Boxed warning)

Serious and sometimes fatal hypersensitivity reactions have been associated with ASPEN ABACAVIR 300 and other abacavir-containing products. This is characterised by the appearance of symptoms indicating multi-organ/body system involvement. Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with ASPEN ABACAVIR 300, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of a hypersensitivity reaction.

Screening is also recommended prior to reinitiation of ASPEN ABACAVIR 300 in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, treatment with an abacavir-containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances when the potential benefit outweighs the risk.

HLA-B*5701-negative patients may develop a hypersensitivity reaction to ASPEN ABACAVIR 300; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Regardless of HLA-B*5701 status, patients who develop a hypersensitivity reaction must permanently discontinue ASPEN ABACAVIR 300 and MUST not be re-challenged with ASPEN ABACAVIR 300.

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 ASPEN ABACAVIR 300.

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

Skin: rash (usually maculopapular or urticarial).

Gastrointestinal tract: nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration.

Respiratory tract: dyspnoea, sore throat, cough or pharyngitis.

Miscellaneous: fever, fatigue, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis.

Neurological/psychiatry: headache, paraesthesia.

Haematological: lymphopenia.

Liver/pancreas: elevated liver function tests, hepatic failure.

Musculoskeletal: myalgia, myolysis, arthralgia, elevated creatine phosphokinase.

Urology: elevated creatinine, renal failure.

Lactic acidosis

Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues.

Early symptoms (symptomatic hyperlactatemia) 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 ASPEN ABACAVIR 300 should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering ASPEN ABACAVIR 300 to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicines and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk. Patients at increased risk should be followed closely.

Use of ASPEN ABACAVIR 300 can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase. In patients with suspicious symptoms or biochemistry measure the venous lactate level (normal < 2 mmol/L) and respond as follows:

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

The above lactate values may not be applicable to paediatric patients. Caution should be exercised when administering ASPEN ABACAVIR 300 to patients with known risk factors for liver disease. Treatment with ASPEN ABACAVIR 300 should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Lipodystrophy and metabolic abnormalities

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

While all members of the Protease Inhibitors and NRTI classes of medicinal products have been

associated with one or more of these specific adverse reactions, linked to a general syndrome commonly referred to as lipodystrophy, there are differences in the risk between individual members of the respective therapeutic classes. In addition the lipodystrophy syndrome has a multi-factorial aetiology, with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles. The long-term consequences of these events are currently unknown. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune reconstitution inflammatory syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART), including ASPEN ABACAVIR 300. Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation.

IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, *Cytomegalovirus retinitis*, *Mycobacterium avium*, *Pneumocystis jiroveci* pneumonia (PCP) and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued.

Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions;

however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic Infections

Patients receiving ASPEN ABACAVIR 300 therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by healthcare providers experienced in the treatment of these associated HIV diseases. Regular monitoring of viral load and CD4 count needs to be done.

Myocardial Infarction

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including ASPEN ABACAVIR 300, and action taken to minimise all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, with ASPEN ABACAVIR 300, 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.

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.

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 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 ASPEN ABACAVIR 300. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of ASPEN ABACAVIR 300 until diagnosis of pancreatitis is excluded.

Liver disease

Use of ASPEN ABACAVIR 300 can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of ASPEN ABACAVIR 300 has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines. Patients with pre-existing liver dysfunction including chronic active

hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

The use of ASPEN ABACAVIR 300 in patients with moderate or severe hepatic impairment is not recommended (see CONTRAINDICATIONS).

Severe hepatomegaly with steatosis

Particular caution should be exercised when administering ASPEN ABACAVIR 300 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 ASPEN ABACAVIR 300 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).

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

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 package inserts for these medicines.

Patients co-infected with HIV and HBV who discontinue ASPEN ABACAVIR 300 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.

Other

Caution should be excercised when ASPEN ABACAVIR 300 and ribavirin are co-administered (see INTERACTIONS).

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

Renal disease

ASPEN ABACAVIR 300 should not be administered to patients with end stage renal disease (see PHARMACOLOGICAL ACTION).

Effects on ability to drive and use machines

Since adverse reactions such as headache, migraine and lack of energy have been reported in patients receiving ASPEN ABACAVIR 300, patients should not drive, use machinery or perform any task that require concentration, until they are certain that ASPEN ABACAVIR 300 does not adversely affect your ability to do so (see SIDE EFFECTS).

INTERACTIONS

Cytochrome P450 3A4 enzyme

Based on the known major metabolic pathways of abacavir, the potential for interactions involving ASPEN ABACAVIR 300 is low. ASPEN ABACAVIR 300 shows no potential to inhibit metabolism mediated by the cytochrome P450 3A4 enzyme.

It has also been shown not to interact with medicines that are metabolised by CYP3A4,

CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for medicine interactions with antiretroviral protease inhibitors and other medicines metabolised by major P450 enzymes.

Enzymatic inducers

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

Ethanol

The metabolism of ASPEN ABACAVIR 300 is altered by concomitant ethanol resulting in an increase in AUC of ASPEN ABACAVIR 300 of about 41 %. Ethanol decreases the elimination of abacavir causing an increase in overall exposure.

No dose reduction of ASPEN ABACAVIR 300 is necessary. ASPEN ABACAVIR 300 has no effect on the metabolism of ethanol.

Methadone

In a pharmacokinetic study, co-administration of 600 mg ASPEN ABACAVIR 300 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 ASPEN ABACAVIR 300 increased the mean methadone systemic clearance by 22 %. The change is not considered clinically relevant for the majority of patients, however occasionally methadone re-titration may be required.

Retinoids

Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction

with ASPEN ABACAVIR 300 is possible but has not been studied.

Tenofovir disoproxil fumarate and lamivudine

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when abacavir was combined with tenofovir disoproxil fumarate and lamivudine as a once daily regimen (see WARNINGS AND SPECIAL PRECAUTIONS).

Ribavirin

Caution should be exercised when ASPEN ABACAVIR 300 and ribavirin are co-administered (see WARNINGS AND SPECIAL PRECAUTIONS).

HUMAN REPRODUCTION

Pregnancy

ASPEN ABACAVIR 300 is contraindicated in pregnancy and lactation (see CONTRAINDICATIONS).

Lactation

ASPEN ABACAVIR 300 is excreted into human milk. Mothers should not breastfeed their babies while receiving treatment with ASPEN ABACAVIR 300. Additionally, it is recommended that HIV infected women do not breastfeed their infants in order to avoid transmission of HIV.

DOSAGE AND DIRECTIONS FOR USE

Adults and adolescents over 12 years

Before starting ASPEN ABACAVIR 300, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir. The recommended dose of ASPEN ABACAVIR 300 is 1 tablet

twice daily. This may be taken as either 300 mg (one tablet) twice a day, or 600 mg (two tablets) once a day.

ASPEN ABACAVIR 300 is not suitable for children < 12 years of age.

ASPEN ABACAVIR 300 can be taken with or without food.

ASPEN ABACAVIR 300 is a tablet formulation for adult dosage.

ASPEN ABACAVIR 300 tablets should not be broken.

Oral solutions are available on the market for administration to children, and for those patients for whom the tablets are inappropriate.

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Renal impairment

No dosage adjustment of ASPEN ABACAVIR 300 is necessary in patients with renal dysfunction (see PHARMACOLOGICAL ACTION).

Hepatic impairment

Abacavir is metabolised primarily by the liver. There are insufficient data to recommend the use of ASPEN ABACAVIR 300 in patients with impaired hepatic function (see CONTRAINDICATIONS).

SIDE EFFECTS

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

Skin: Rash (usually maculopapular or urticarial)

Gastrointestinal tract: Nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration

Respiratory tract: Dyspnoea, sore throat, cough or pharyngitis, adult respiratory distress syndrome, respiratory failure

Miscellaneous: Fever, fatigue, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis

Neurological/psychiatry: Headache, paraesthesia

Haematological: Lymphopenia

Liver/pancreas: Elevated liver function tests, hepatic failure, hepatitis

Musculoskeletal: Myalgia, myolysis, arthralgia, elevated creatine phosphokinase

Urology: Elevated creatinine, renal failure

Infections and infestations

Less frequent: Ear/nose/throat infections, viral respiratory tract infections, pneumonia

Blood and lymphatic system disorders

Less frequent: Anaemia, neutropenia

Metabolism and nutrition disorders

Frequent: Anorexia

Less frequent: Redistribution/accumulation of body fat (see WARNINGS AND SPECIAL PRECAUTIONS), (the incidence of this event is dependent on multiple factors including the particular antiretroviral combination), combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia

Psychiatric disorders

Frequent: Depressive disorders, dreams/sleep disorders

Less frequent: Anxiety

Nervous system disorders

Frequent: Headache/migraine

Gastrointestinal disorders

Frequent: Diarrhoea, vomiting, nausea

Less frequent: Pancreatitis, abdominal swelling and pain, gastritis

Hepato-biliary disorders

Less frequent: Lactic acidosis/severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders

Frequent: Skin rash (without systemic symptoms)

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

Musculoskeletal, connective tissue and bone disorder

Less frequent: Osteonecrosis, rhabdomyolysis

General disorders and administrative site conditions

Frequent: Lethargy, fatigue, fever, malaise, chills

Investigations

Less frequent: Elevated blood glucose and triglyceride concentrations, liver function test

abnormalities, and CPK elevations

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

If overdosage occurs the patient should be monitored for evidence of toxicity (see SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS).

Treatment

Standard supportive treatment applied as necessary. It is not known whether abacavir, as contained in ASPEN ABACAVIR 300, can be removed by peritoneal dialysis or haemodialysis.

IDENTIFICATION

A dark-yellow coloured, film-coated biconvex, capsule-shaped tablet, “AB” engraved on one side and break-line on the other side.

PRESENTATION

ASPEN ABACAVIR 300 tablets are available in pack sizes of 60 tablets in:

- White, opaque HDPE containers with child-resistant, polypropylene, screw closure & layered induction sealing liner. *OR*
- Blister packs of silver aluminium foil and amber PVC film packed into cardboard cartons.

Not all packs and pack sizes will necessarily be marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep container tightly closed.

Keep blister in carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ASPEN ABACAVIR 300: 43/20.2.8/0724

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

PHARMACARE LIMITED

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

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