ABACAVEX (Abacavir Oral Solution USP 20 mg/ml)
ABACAVEX (Abacavir Tablets USP 300 mg)

Abacavir Sulfate Oral Solution 20mg/ml: Description and composition:

Clear to opalescent yellowish, strawberry-banana flavoured liquid. Each ml contains abacavir 20mg as abacavir sulfate.

Abacavir Sulfate Tablets USP 300mg

Description and composition:

Yellow colored, biconvex, capsule shaped, coated tablet, debossed with 'D' and '88' on either side of the score line on one side and plain with a score line on other side.

Each film coated tablet contains: Abacavir Sulfate equivalent to Abacavir 300mg.

Pharmacodynamics:

Pharmacotherapeutic group: Nucleoside reverse transcriptase inhibitors, ATC Code: J05A F06 Abacavir is a NRTI. It is a potent selective inhibitor of HIV-1 and HIV-2, including HIV-1 isolates with reduced susceptibility to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine. Abacavir is metabolised intracellularly to the active moiety, carbovir 5â€™- 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, 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 IC50 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 PIs or NNRTIs is unlikely. Reduced susceptibility to abacavir in patients with uncontrolled viral replication, who have been pretreated 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.

Additional information:

The safety and efficacy of abacavir tablets in a number of different multidrug combination regimens is still not completely assessed (particularly in combination with NNRTIs).

Abacavir penetrates the cerebrospinal fluid (CSF), and has been shown to reduce HIV-1 RNA levels in the CSF.

However, no effects on neuropsychological performance were seen when it was administered to patients with AIDS dementia complex.

Pharmacokinetics:

Absorption: Abacavir is rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83%. Following oral administration, the mean time (Tmax) 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 Cmax and Cmin of abacavir are approximately 3.00 Î¼g/ml (30%) and 0.01 Î¼g/ml (99%), respectively. The mean (CV) AUC over a dosing interval of 12 hours was 6.02 Î¼g.h/ml (29%), equivalent to a daily AUC of approximately 12.0 Î¼g.h/ml. The Cmax value for the oral solution is slightly higher than the tablet. After a 600 mg abacavir tablet dose, the mean (CV) abacavir Cmax was approximately 4.26 Î¼g/ml (28%) and the mean AUC was 11.95 Î¼g.h/ml (21%).

Food delayed absorption and decreased Cmax but did not affect overall plasma concentrations (AUC). Therefore abacavir tablets can be taken with or without food.

Administration of crushed tablets with a small amount of semi-solid food or liquid would not be expected to have an impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic data, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Distribution: Following intravenous administration, the apparent volume of distribution was about 0.8 l/kg, indicating that abacavir penetrates freely into body tissues.

Biotransformation: 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 in patients with mild hepatic impairment.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: Abacavir is rapidly 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 abacavir 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.

Elderly: The pharmacokinetics of abacavir have not been studied in patients over 65 years of age.

Indications:

Indicated in antiretroviral combination therapy, for, the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children.

Recommended Dose:

Abacavir Sulfate Oral solution:

Adults and adolescents weighing at least 30kg: The recommended dose of abacavir sulfate oral solution is 600 mg daily (30 ml). This may be administered as either 300 mg (15 ml) twice daily or 600 mg (30 ml) once daily.

Patients changing to the once daily regimen should take 300 mg (15 ml) twice a day and switch to 600 mg (30 ml) once a day the following morning. Where an evening once daily regimen is preferred, 300 mg (15 ml) of abacavir sulfate oral solution should be taken on the first morning only, followed by 600 mg (30 ml) in the evening. When changing back to a twice daily regimen, patients should complete the day's treatment and start 300 mg (15 ml) twice a day the following morning.

Children from three months and weighing less than 30kg: The recommended dose is 8 mg/kg twice daily up to a maximum of 600 mg (30 ml) daily.

Children less than three months: The data available on the use of abacavir sulfate oral solution in this age group are very limited.

Abacavir sulfate oral solution can be taken with or without food. Tablet formulation of abacavir sulfate is available.

Renal impairment: No dosage adjustment of abacavir sulfate oral solution is necessary in patients with renal dysfunction. However, abacavir sulfate oral solution 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 abacavir is not recommended unless judged necessary. In patients with mild and moderate hepatic impairment close monitoring is required, and if feasible, monitoring of abacavir plasma levels is recommended. Abacavir is contraindicated in patients with severe hepatic impairment.

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

Abcavir Sulfate Tablets USP 300mg:

Therapy should be initiated by a physician experienced in the management of HIV infection. Abacavir Tablets can be taken with or without food.To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing.For patients who are unable to swallow tablets,Abacavir is available as an oral solution. Alternatively, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately *(see Pharmacokinetics).*

Adults, adolescents and children weighing at least 25 kg :

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

Children from three months and weighing less than 25 kg :

Children weighing 14 to < 20 kg: one-half of a scored abacavir tablet twice daily.

Children weighing ≥ 20 kg to < 25 kg:

One-half of a scored abacavir tablet taken in the morning and one whole tablet taken in the evening.

Children weighing at least 25 kg:

The adult dosage of 300 mg twice daily or 600 mg once daily should be taken.The oral solution may be administered to children weighing less than 14 kg or those who are unable to swallow tablets.

Children less than three months

The data available on the use of Abacavir in this age group are very limited *(see Pharmacokinetics).*

Renal impairment

No dosage adjustment of Abacavir is necessary in patients with renal dysfunction *(see Pharmacokinetics).* Abacavir should be avoided in patients with end-stage renal disease.

Hepatic impairment

Abacavir is metabolised primarily by the liver. The recommended dose of Abacavir Tablets in patients with mild hepatic impairment is 200 mg (10 ml) twice a day. To enable dose reduction Abacavir oral solution should be used for the treatment of these patients. Pharmacokinetic and safety data on the use of abacavir in patients with moderate and severe hepatic impairment are not available *(see Pharmacokinetics)* Therefore the use of Abacavir is not recommended in patients with moderate or severe hepatic impairment, unless the benefit of us outweighs the risk.

Route of administration:

Oral

Contraindications:

Abacavir sulfate oral solution is contraindicated in patients with known hypersensitivity to abacavir or to any of the excipients of abacavir sulfate oral solution

Abacavir sulfate oral solution is contraindicated in patients with severe hepatic impairment.

Abacavir tablets are contraindicated in patients with known hypersensitivity to abacavir or to any of the excipients of abacavir tablets.

Abacavir tablets are contraindicated in patients with severe hepatic impairment.

Warning & Precautions:

Hypersensitivity reaction:

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. It is noteworthy that among patients with a clinically suspected hypersensitivity reaction, a proportion did not carry HLA-B*5701. Therefore, even in the absence of 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.

Skin patch testing was used as a research tool for the PREDICT-1 study but has no utility in the clinical management of patients and therefore should not be used in the clinical setting.

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 Abacavir Tablets.

Clinical Management

Hypersensitivity reaction symptoms usually appear within the first six weeks of initiation of treatment with abacavir, although these reactions may occur at any time during therapy. Patients should be monitored closely, especially during the first two months of treatment with Abacavir Tablets, with consultation every two weeks.

Regardless of their HLA-B*5701 status, patients who are diagnosed with a hypersensitivity reaction whilst on therapy MUST discontinue Abacavir Tablets immediately.

Abacavir Tablets, or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir), MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction. Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, Abacavir 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).

Special care is needed for those patients simultaneously starting treatment with Abacavir Tablets and other medicinal products known to induce skin toxicity (such as non-nucleoside reverse transcriptase inhibitors -NNRTIs). This is because it is currently difficult to differentiate between rashes induced by these products and abacavir related hypersensitivity reactions.

Management after an interruption of Abacavir Tablets therapy

Regardless of a patient's HLA-B*5701 status, if therapy with Abacavir 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, Abacavir Tablets or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir) must not be restarted.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting Abacavir Tablets in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping Abacavir 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 Abacavir 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 abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir 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 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 a HLA-B*5701 negative patient can also experience an abacavir hypersensitivity reaction. Therefore, ANY patient who develops signs or symptoms consistent with a hypersensitivity reaction to abacavir. MUST CONTACT THEIR DOCTOR IMMEDIATELY.
- Patients who are hypersensitive to abacavir should be reminded that they must never take Abacavir Tablets or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir) again, regardless of their HLA-B*5701 status.
- in order to avoid restarting Abacavir Tablets, patients who have experienced a hypersensitivity reaction should be asked to return the remaining Abacavir Tablets or oral solution to the pharmacy. Patients who have stopped Abacavir 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 Package Leaflet included in the Abacavir Tablets 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.

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 nucleoside analogues 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 nucleoside analogues 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.

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 HIVnegative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). 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 nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

A/s: 280 x 600 mm ■ Black

AUROBINDO Packaging Development	Product Name: Abacavir Sulfate Tablets	Component: Leaflet	Item Code: P1529210	Date & Time: 16.02.2023 & 11.00 am
	Customer / Country: Malaysia_Unit 3	Version No.: 06	Reason Of Issue: NEW	Reviewed / Approved by
Team Leader: Lovaraju	Dimensions: 280 x 600 mm	No. of Colours : 01		
Initiator: Subramanyam				
Artist: SCD	Pharmacode: 29210	29210		
Additional Information : Word file added & Dimension Changed				Sign / Date

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 drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Pancreatitis: pancreatitis has been reported, but a causal relationship to abacavir 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 abacavir was combined with tenofovir disoproxil fumarate and lamivudine as a once daily regimen.

Liver disease: The safety and efficacy of Abacavir Tablets has not been established in patients with significant underlying liver disorders.

Abacavir Tablets is contraindicated in patients with severe hepatic impairment.

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.

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

Caution should be exercised when abacavir and ribavirin are co-administered.

Renal disease: Abacavir Tablets should not be administered to patients with end-stage renal disease.

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 carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves™ disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and 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.

Opportunistic infections: patients receiving Abacavir Tablets 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 physicians experienced in the treatment of these associated HIV diseases.

Transmission: patients should be advised that current antiretroviral therapy, including Abacavir Tablets, 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.

Myocardial Infarction: An association between myocardial infarction and the use of abacavir showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall 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 Abacavir Tablets, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Drug Interactions with other medicaments:

The potential for drug interactions involving abacavir is low. *In vitro* studies have shown that abacavir has potential to inhibit cytochrome P450 1A1 (CYP1A1). Abacavir shows limited potential to inhibit metabolism mediated by the CYP3A4 enzyme. It has also been shown *in vitro* not to interact with drugs that are metabolised by CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for drug interactions with antiretroviral protease inhibitors and other drugs metabolised by major CYP enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine and lamivudine.

Effect of Abacavir on the Pharmacokinetics of Other Agents

In vitro, abacavir demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance protein (BCRP) or P-glycoprotein (Pgp) and minimal inhibition of organic cation transporter 1 (OCT1), OCT2 and multidrug and toxin extrusion protein 2-K (MATE2-K). Abacavir is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Abacavir is an inhibitor of MATE1 in vitro, however abacavir has low potential to affect the plasma concentrations of MATE1 substrates at therapeutic drug exposures (up to 600 mg).

Effect of Other Agents on the Pharmacokinetics of Abacavir

In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, Multidrug resistance-associated protein 2 (MRP2) or MRP4, therefore drugs that modulate these transporters are not expected to affect abacavir plasma concentrations.

Although abacavir is a substrate of BCRP and Pgp *in vitro,* clinical studies demonstrate no clinically significant changes in abacavir pharmacokinetics when co-administered with lopinavir/ritonavir (Pgp and BCRP inhibitors).

Interactions relevant to abacavir

Ethanol: The metabolism of abacavir is altered by concomitant ethanol 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, coadministration of 600 mg *ZIAGEN* twice daily with 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 re-titration may be required.

Retinoids: Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

Riociguat: *In vitro,* abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving the combination of abacavir/dolutegravir/lamivudine (600mg/50mg/300mg once daily) led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy subjects. Riociguat dose may need to be reduced, consult the riociguat product labeling for dosing recommendations.

Side effects:

For many of the other adverse events reported, it is unclear whether they are related to *ZIAGEN,* to the wide range of medicinal products used in the management of HIV disease or as a result of the disease process.

Many of those listed below (nausea, vomiting, diarrhoea, fever, fatigue, rash) occur commonly as part of *ZIAGEN* hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction. If *ZIAGEN* has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart *ZIAGEN*, this should be done only under direct medical supervision *(see Warnings and Precautions - "Special considerations following an interruption of ZIAGEN therapy")*.

The majority of the adverse reactions listed below have not been treatment limiting. The following convention has been used for their classification: very common (more than 1/10), common (more than 1/100, less than 1/10), uncommon (more than 1/1,000, less than 1/100), rare (more than 1/10,000, less than 1/1,000) very rare (less than 1/10,000).

Clinical Trial Data

Metabolism and nutrition disorders

Common: anorexia.

Nervous system disorders

Common: headache.

Gastrointestinal disorders

Common: nausea, vomiting, diarrhoea.

General disorders and administration site disorders

Common: fever, lethargy, fatigue.

In controlled clinical studies laboratory abnormalities related to *ZIAGEN* treatment were uncommon, with no differences in incidence observed between *ZIAGEN* treated patients and the control arms.

Paediatric population

The safety database to support abacavir once daily dosing in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects received abacavir and lamivudine either once or twice daily *(see Clinical Studies).* No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Postmarketing Data

Metabolism and nutrition disorders

Common: hyperlactataemia.

Rare: lactic acidosis *(see Warnings and Precautions).*

Gastrointestinal disorders

Rare: pancreatitis has been reported, but a causal relationship to ZIAGEN treatment is uncertain.

Skin and subcutaneous tissue disorders

Common: rash (without systemic symptoms).

Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Description of Selected Adverse Reactions

Hypersensitivity (see also Warnings and Precautions):

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:	**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, fatigue, malaise,** oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry:	**Headache,** paraesthesia
Haematological:	Lymphopenia
Liver/pancreas:	**Elevated liver function tests,** hepatic failure
Musculoskeletal:	**Myalgia,** rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology:	Elevated creatinine, renal failure

Pregnancy and Lactation:

Pregnancy

Abacavir Tablets is not recommended during pregnancy. The safe use of abacavir 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 (see section 5.3). The teratogenic potential of abacavir could not be established from studies in animals.

Breast-feeding:

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 abacavir.

Additionally, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Symptoms and treatment of Overdosage:

Single doses up to 1200 mg and daily doses up to 1800 mg of abacavir have been administered to patients in clinical studies. No unexpected adverse reactions were reported. 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.

Storage condition:

Store in a dry place, below 30°C and protect from light

Shelf life:

Abacavir Sulfate oral solution 20mg/ml: 24 months.

Abacavir Sulfate Tablets USP 300mg: 36 months

Presentation:

Abacavir sulfate oral solution is supplied in HDPE bottles containing 240ml of oral solution. An oral dosing syringe with adaptor or measuring cup is included in the pack.

Abacavir Sulfate Tablets USP 300mg is available in plastic container contains 60 tablets.

PRODUCT REGISTRATION HOLDER IN MALAYSIA:

UNIMED SDN BHD,
53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara, 52200,
Kuala Lumpur, Malaysia.

Manufactured by:

Aurobindo Pharma Limited
Unit - III, Survey. No. 313 & 314,
Bachupally, Bachupally Mandal,
Medchal-Malkajgiri District,
Telangana State, 500090, India

Date of revision of the text: July 2022

P1529210