

DATA SHEET

ZIAGEN[®] Tablets

Each tablet contains 300mg of abacavir as abacavir sulphate

Presentation

The scored film-coated tablets are yellow, biconvex, and capsule shaped. They are engraved with "GX 623" on both sides. Each tablet contains 300 mg abacavir base as the sulphate salt.

Uses

Actions

Pharmacotherapeutic group – nucleoside analogue.

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

In a study of 20 HIV-infected patients receiving abacavir 300mg twice daily, with only one 300mg dose taken prior to the sampling time, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 hours, compared to the geometric mean abacavir plasma half-life in this study of 2.6 hours. Similar intracellular kinetics are expected from abacavir 600mg once daily. These data support the use of abacavir 600mg once daily for the treatment of HIV infected patients. Additionally, the efficacy of this combination given once daily has been demonstrated in a pivotal clinical study (CNA30021- See Clinical experience).

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 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.

Clinical experience: In clinical studies, treatment with ZIAGEN in combination with zidovudine and lamivudine was associated with significant and sustained reductions in viral load, with corresponding rises in CD4 cell count in adults and children.

In a double-blind clinical study over 48 weeks in treatment naïve adult patients, the combination of abacavir, lamivudine and zidovudine showed an equivalent antiviral effect to the combination with indinavir, lamivudine and zidovudine in the primary analysis of efficacy. In a secondary analysis of patients with baseline plasma HIV-1 RNA levels above 100,000 copies per mL, patients receiving the combination containing indinavir had a superior response. Patients with baseline plasma HIV-1 RNA below 100,000 copies per mL had an equivalent response to both treatments.

A once daily regimen of abacavir was investigated in a multicentre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. They were randomised to receive either abacavir 600mg once daily or 300mg twice daily, both in combination with lamivudine 300mg once daily and efavirenz 600mg once daily. Patients were stratified at baseline based on plasma HIV-1 RNA \leq 100,000 copies/mL or $>$ 100,000 copies/mL. The duration of double-blind treatment was at least 48 weeks. The results are summarised in the table below:

**Virological Response Based on Plasma HIV-1 RNA $<$ 50 copies/mL at
Week 48
ITT-Exposed Population**

Populations	ABC once/day + 3TC + EFV (N = 384)	ABC twice/day + 3TC + EFV (N = 386)
Sub-group by baseline RNA		
\leq 100,000 copies/mL	141/217 (65%)	145/217 (67%)
$>$ 100,000 copies/mL	112/167 (67%)	116/169 (69%)
Total population	253/384 (66%)	261/386 (68%)

The abacavir once daily group was demonstrated to be non-inferior when compared to the twice daily group in the overall and base-line viral load sub-groups. The incidence of adverse events reported were similar in the two treatment groups.

Genotypic analysis was attempted for all subjects with virologic failure (confirmed HIV RNA >50 copies/mL). There was a low overall incidence of virologic failure in both the once and twice daily treatment groups (10% and 8% respectively). Additionally for technical reasons genotyping was restricted to samples with plasma HIV-1 RNA >500 copies/mL. This resulted in a small sample size. Therefore no firm conclusions could be drawn regarding differences in treatment emergent mutations between the two treatment groups. Reverse transcriptase amino acid residue 184 was consistently the most frequent position for NRTI resistance-associated mutations (M184V or M184I). The second most frequent mutation was L74V. Mutations Y115F and K65R were uncommon.

In a study comparing unblinded NRTI combinations (with or without blinded nelfinavir) in children, a significantly greater proportion treated with abacavir and lamivudine (73%) or abacavir and zidovudine (70%) had HIV-1 RNA \leq 400 copies/mL at 24 weeks, compared with those treated with lamivudine and zidovudine (44%). In children with extensive antiretroviral exposure, a modest but sustained effect of the combination of abacavir, lamivudine and zidovudine was observed.

In therapy experienced patients, limited data show that the addition of ZIAGEN to nucleoside reverse transcriptase inhibitors provides additional benefit in reducing viral load, and increasing CD4 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.

Abacavir penetrates the cerebrospinal fluid (CSF) (see Pharmacokinetic Properties), and has been shown to reduce HIV-1 RNA levels in the CSF. In combination with other antiretrovirals it may have a role in the prevention of HIV related neurological complications, and may delay the development of resistance in this sanctuary site.

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 (t_{max}) to maximal serum concentrations of abacavir is about 1.5 hours for the tablet formulation and about 1.0 hour for the solution formulation.

There are no differences observed between the AUC for the tablet or solution. At a dosage of 300mg twice daily, the mean steady state C_{max} of abacavir from tablet administration was 3.00 μ g/mL, and the mean AUC over a dosing interval of 12 hours was 6.02 μ g.h/mL (daily AUC of approximately 12.0 μ g.h/mL). The C_{max} value for the oral solution is slightly higher than the tablet. After a 600mg abacavir tablet dose, the mean abacavir C_{max} was approximately 4.26 μ g/mL and the mean AUC was 11.95 μ g.h/mL.

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

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

Studies in HIV infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%. In a Phase I pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300mg twice a day. The mean concentration of abacavir achieved in the CSF 1.5 hours post dose was 0.14mcg/mL. In a further pharmacokinetic study of 600mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0.13mcg/mL at 0.5 to 1 hour after dosing, to approximately 0.74mcg/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 IC50 of abacavir of 0.08mcg/mL or 0.26microM.

Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (circa 49%) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for drug 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 administered dose. These metabolites are excreted in the urine.

Elimination: The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300mg twice a day there is no significant drug 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.

Pharmacokinetics of special populations:

Hepatically impaired: Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6). 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.

In order to achieve exposures that are within the therapeutic range of patients without liver disease, patients with mild hepatic impairment should receive 200mg abacavir twice daily. The pharmacokinetics have not been studied in patients with moderate or severe hepatic impairment, therefore Ziagen is contra-indicated in these patient groups.

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.

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 slightly greater variability in plasma concentrations. The recommended dose for children from three months to 12 years is 8mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve therapeutic concentrations equivalent to 300mg twice a day in adults.

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

Indications

ZIAGEN is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children.

Dosage and Administration

Adults and adolescents over 12 years: the recommended dose of ZIAGEN is 600mg daily. This may be administered as either 300mg (one tablet) twice daily or 600mg (two tablets) once daily.

Children from three months to 12 years: the recommended dose is 8mg/kg twice daily up to a maximum of 600mg daily.

Children less than three months: the data available on the use of ZIAGEN in this age group are very limited (see Pharmacokinetic properties).

ZIAGEN can be taken with or without food.

ZIAGEN is available as an oral solution for use in children and for those patients for whom the tablets are inappropriate.

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

Renal impairment: No dosage adjustment of ZIAGEN is necessary in patients with renal dysfunction (see Pharmacokinetic properties).

Hepatic impairment: Abacavir is metabolised primarily by the liver. The recommended dose of ZIAGEN in patients with mild hepatic impairment (Child-Pugh score 5-6) is 200mg twice a day. To enable dose reduction Ziagen oral solution should be used for the treatment of these patients. ZIAGEN is contra-indicated in patients with moderate or severe hepatic impairment, as the pharmacokinetics have not been studied in these patient groups (see Pharmacokinetic Properties).

Contraindications

ZIAGEN is contra-indicated in patients with known hypersensitivity to abacavir or any ingredient of ZIAGEN tablets.

ZIAGEN is contra-indicated in patients with moderate or severe hepatic impairment.

Warnings and Precautions

Hypersensitivity: (See also Adverse Effects)

In clinical studies approximately 5% of subjects receiving ZIAGEN developed a hypersensitivity reaction, which in rare cases 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.

Clinicians must screen for carriage of the HLA-B*5701 allele in any HIV-infected patient prior to the commencement of abacavir therapy, or prior to recommencement of abacavir therapy. Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and with close medical supervision.

In any patient treated with abacavir, the clinical diagnosis of suspected

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

- **Clinical Description**

The hypersensitivity reaction is characterised by the appearance of symptoms indicating multi-organ involvement. The majority of patients have fever and/or rash as part of the syndrome.

Some of the other symptoms of hypersensitivity may include fatigue, malaise, gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and respiratory signs and symptoms such as dyspnoea, sore throat, cough and abdominal chest x-ray findings (predominantly infiltrates, which can be localised). **The symptoms of this hypersensitivity reaction can occur at any time during treatment with ZIAGEN**, 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 ZIAGEN.

- **Clinical Management**

Patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed ZIAGEN MUST be discontinued immediately. ZIAGEN, or any other medicinal product containing abacavir (Kivexa® Trizivir®), 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, ZIAGEN should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reaction to other medications). ZIAGEN, or any other medicinal product containing abacavir (Kivexa® Trizivir®), should not be re-started even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

An alert card with information for the patient about this hypersensitivity reaction is included in the ZIAGEN pack.

- **Special considerations following an interruption of ZIAGEN therapy**

If therapy with ZIAGEN has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If hypersensitivity reaction cannot be ruled out, ZIAGEN, or any other medicinal product containing abacavir (Kivexa® Trizivir®) should not be**

restarted, irrespective of HLA*B5701 carrier status.

There have been infrequent reports of hypersensitivity reaction following reintroduction of ZIAGEN, 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 ZIAGEN in these patients, this should be done only under direct medical supervision.

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to re-start ZIAGEN, this must be done only if medical care can be accessed readily by the patient.

- **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.
- 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 ZIAGEN or any other medicinal product containing abacavir (Kivexa ® Trizivir®) again.
- In order to avoid restarting ZIAGEN, patients who have experienced a hypersensitivity reaction should be asked to return the remaining ZIAGEN tablets or oral solution to the pharmacy.
- Patients who have stopped Ziagen 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 ZIAGEN 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/Severe Hepatomegaly with Steatosis - Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including abacavir. A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea

and tachypnoea). Caution should be exercised when administering ZIAGEN to any patient, and particularly to those with known risk factors for liver disease. Treatment with ZIAGEN should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Fat redistribution – Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy (see Adverse Effects).

Whilst all members of the PI and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that 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.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reconstitution Syndrome: In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral 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 cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and Pneumocystis jirovecii (P. carinii) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

Opportunistic infections - Patients receiving ZIAGEN 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 ZIAGEN, 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: 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 GSK sponsored clinical trials no excess risk of myocardial infarction was observed with abacavir use. There is no known biological mechanism to explain a potential increase. In totality the available data from observational cohorts and from controlled clinical trials are inconclusive in regard to the relationship between abacavir treatment and the risk of myocardial infarction.

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

Pregnancy and Lactation

Pregnancy: The safe use of ZIAGEN in human pregnancy has not been established. Abacavir has been associated with findings in animal reproductive studies (see Pre-clinical Safety Data). Therefore administration of ZIAGEN in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the foetus.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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

Effects on Ability to Drive and Use Machines

No currently available data suggests that ZIAGEN affects the ability to drive or operate machinery.

Adverse Effects

Hypersensitivity: (See also Warnings and Precautions)

In clinical studies, approximately 5% of subjects receiving ZIAGEN developed a hypersensitivity reaction, which in rare cases has proved fatal. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

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

Symptoms can occur at any time while being treated with ZIAGEN, but usually appear within the first six weeks of initiation of treatment (median time to onset 11 days).

The signs and symptoms of this hypersensitivity reaction are listed below. Those reported **in at least 10% of patients** with a hypersensitivity reaction are in bold text.

<i>Skin:-</i>	Rash (usually maculopapular or urticarial)
<i>Gastrointestinal tract:-</i>	Nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration
<i>Respiratory tract:-</i>	Dyspnoea, cough, sore throat, adult respiratory distress syndrome, respiratory failure
<i>Miscellaneous:-</i>	Fever, fatigue, malaise, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
<i>Neurological/Psychiatry:-</i>	Headache, paraesthesia
<i>Haematological:-</i>	Lymphopenia
<i>Liver/pancreas:-</i>	Elevated liver function tests, hepatic failure
<i>Musculoskeletal:-</i>	Myalgia, rarely myolysis, arthralgia, elevated creatine phosphokinase
<i>Urology:-</i>	Elevated creatinine, renal failure

Some patients with hypersensitivity were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis) a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in ZIAGEN being continued or re-introduced, leading to a more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. If hypersensitivity reaction can not be ruled

out, ZIAGEN or any other medicinal product containing abacavir (Kivexa® Trizivir®) should not be restarted.

The symptoms related to this hypersensitivity reaction worsen with continued therapy, and usually resolve upon discontinuation of ZIAGEN.

Restarting ZIAGEN following a hypersensitivity reaction results in a prompt return of symptoms within hours. **This recurrence of the hypersensitivity reaction may be more severe than on initial presentation, and may include life-threatening hypotension and death. Patients who develop this hypersensitivity reaction must discontinue ZIAGEN and must never be rechallenged with ZIAGEN, or any other medicinal product containing abacavir (Kivexa® Trizivir®), irrespective of HLA*B5701 carrier status.**

There have been infrequent reports of hypersensitivity reactions following reintroduction of ZIAGEN, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal or a respiratory symptom).

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction.

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 abacavir 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 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 (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000).

Metabolism and nutrition disorders

Common: anorexia, hyperlactataemia

Rare: lactic acidosis (see Warnings and Precautions).

Redistribution/accumulation of body fat (see Warnings and Precautions). The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

Nervous system disorders

Common: headache

Gastrointestinal disorders

Common: nausea, vomiting, diarrhoea

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

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.

Interactions

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for drug interactions involving abacavir is low. Abacavir shows no potential to inhibit metabolism mediated by the cytochrome P₄₅₀ 3A4 enzyme. It has also been shown *in vitro* not to interact with drugs that are metabolised by CYP 3A4, 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 P₄₅₀ enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

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 600mg abacavir twice daily with methadone showed a 35% reduction in abacavir C_{max} and a one hour delay in t_{max}, but the AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study abacavir increased the mean methadone systemic clearance by 22%. 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.

Overdosage

Single doses up to 1200mg and daily doses up to 1800mg 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 (see Adverse Effects), and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

Pharmaceutical Precautions

Incompatibilities

None known.

Shelf Life

3 years.

Special Precautions for Storage

Store below 30°C.

Instructions for Use/Handling

None required.

Medicines Classification

Prescription Medicine

Package Quantities

ZIAGEN Tablets are available in polyvinyl chloride/foil blister packs containing 60 tablets.

Further Information

List of Excipients

Core: Microcrystalline cellulose, sodium starch glycollate, magnesium stearate, colloidal anhydrous silica.

Coating: Triacetin, methylhydroxypropylcellulose, titanium dioxide, polysorbate 80, iron oxide yellow.

Preclinical Safety Data

Mutagenicity and carcinogenicity: Abacavir was not mutagenic in bacterial tests but showed activity *in vitro* in the human lymphocyte chromosome aberration assay, the mouse lymphoma assay, and the *in vivo* micronucleus test. This is consistent with the known activity of other nucleoside analogues. These results indicate that abacavir is a weak clastogen both *in vitro* and *in vivo* at high test concentrations.

Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver, urinary bladder, lymph nodes and the subcutis of female rats.

The majority of these tumours occurred at the highest abacavir dose of 330mg/kg/day in mice and 600mg/kg/day in rats. These dose levels were equivalent to 24 to 32 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose of 110mg/kg. This is equivalent to six times the expected human systemic exposure. There is no structural counterpart for this gland in humans. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

Repeat-dose toxicity: Mild myocardial degeneration in the heart of mice and rats was observed following administration of abacavir for two years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

Reproductive toxicology: Placental transfer of abacavir and/or its related metabolites has been shown to occur in animals. Evidence of toxicity to the developing embryo and fetuses occurred only in rats at maternally toxic doses of 500mg/kg/day and above. This dose is equivalent to 32 to 35 times human therapeutic exposure based on AUC. The findings included foetal oedema, variations and malformations, resorptions, decreased foetal body weight and an increase in still births. The dose at which there were no effects on pre or post natal development was 160mg/kg/day. This dose is equivalent to an exposure of about 10 times that in humans. Similar findings were not observed in rabbits.

A fertility study in the rat has shown that doses up to 500mg/kg of abacavir had no effect on male or female fertility.

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ALERT CARD

MANDATORY PACKAGING INFORMATION

<p style="text-align: center;">IMPORTANT ALERT CARD ZIAGEN® (abacavir sulfate) tablets Carry this card with you at all times</p>
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Patients taking ZIAGEN may develop a hypersensitivity reaction (serious allergic reaction) which **can be life-threatening** if treatment with ZIAGEN is continued. **CONTACT YOUR DOCTOR IMMEDIATELY for advice on whether you should stop taking ZIAGEN if:**

- 1) You get a skin rash OR
- 2) You get one or more symptoms from at least TWO of the following groups:
 - fever
 - shortness of breath, sore throat or cough
 - nausea or vomiting or diarrhoea or abdominal pain,
 - severe tiredness or achiness or generally ill feeling,

If you have discontinued ZIAGEN due to this reaction, **YOU MUST NEVER** take ZIAGEN or any other medicine containing abacavir (Kivexa® Trizivir®) again, as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

CARTON PANEL

The following text must be included on one of the carton panels:

- **Detach enclosed Alert Card, it contains important safety information**
- **WARNING!** In case of any symptoms suggesting hypersensitivity reactions, contact your doctor **IMMEDIATELY**.
- **“Pull here”** (with Alert Card attached).