ZIAGEN RANGE

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ZIAGEN® TABLETS

ZIAGEN® ORAL SOLUTION

Hypersensitivity to abacavir (see SIDE EFFECTS)

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

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

Risk factors:

Studies have shown that carriage of the HLA B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. In the prospective study CNA106030 (PREDICT-1), use of pretherapy screening for the HLA B*5701 allele and subsequently avoiding abacavir in patients with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7,8 % (66 of 847) to 3,4 %

(27 of 803) ($p < 0,0001$) and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2,7 % (23 of 842) to 0,0 % (0 of 802) ($p < 0,0001$). Based on this study, it is estimated that 48 % to 61 % of patients with the HLA B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0 % to 4 % of patients who do not have the HLA B*5701 allele.

It is recommended that any HIV-infected patient without prior exposure to abacavir be screened for HLA-B*5701 allele.

Screening is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see *Special considerations following an interruption of ZIAGEN therapy*).

Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended.

Clinical description:

The hypersensitivity reaction 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. Some of the other symptoms of hypersensitivity may include fatigue, malaise, gastrointestinal symptoms such as nausea, vomiting, diarrhoea, and abdominal pain and respiratory signs and symptoms such as dyspnoea, sore throat, cough, and abnormal chest X-ray findings (predominantly infiltrates, which can be localised).

The symptoms of this hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks of therapy. The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Clinical management:

Regardless of their HLA-B*5701 status, any patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed ZIAGEN MUST be discontinued immediately. ZIAGEN, or any other medicinal product containing abacavir, MUST NEVER be restarted following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, ZIAGEN should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastro-enteritis or reactions to other medications). ZIAGEN, or any other medicinal product containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

An Alert Card with information for the patient about the hypersensitivity reaction is included in the ZIAGEN pack.

Special considerations following an interruption of ZIAGEN therapy:

Regardless of a patient's HLA-B*5701 status, 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 a hypersensitivity cannot be ruled out, ZIAGEN or any other medicinal product containing abacavir should not be restarted.**

There have been infrequent reports of hypersensitivity reaction following re-introduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory

symptom). If a decision is made to restart ZIAGEN in these patients, this should be done only under direct medical supervision.

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

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

Essential patient information:

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

- Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.
- Patients must also be informed that HLA-B*5701 negative patients can also experience abacavir hypersensitivity reaction. Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir **MUST CONTACT their doctor IMMEDIATELY.**
- Patients who are hypersensitive to abacavir should be reminded that they must never take ZIAGEN or any other medicinal product containing abacavir again, regardless of their HLA-B*5701 status.

- 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 insert 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.

COMPOSITION:

ZIAGEN TABLET: Each tablet contains the equivalent of 300 mg abacavir as abacavir sulphate.

Sugar free.

The tablet core contains colloidal anhydrous silica, magnesium stearate, microcrystalline cellulose and sodium starch glycollate. The tablet coating contains iron oxide yellow, methylhydroxypropylcellulose, polysorbate 80, titanium dioxide and triacetin.

ZIAGEN ORAL SOLUTION: Each millilitre contains the equivalent of 20 mg abacavir as abacavir sulphate.

Preservatives: methyl hydroxybenzoate 0,15 % *m/v*, propyl hydroxybenzoate 0,018 % *m/v.*

Contains sugar (maltodextrin and sorbitol).

Other ingredients: citric acid anhydrous, maltodextrin, methyl parahydroxybenzoate (E218), natural and artificial strawberry and banana flavour, propyl parahydroxybenzoate (E216), propylene glycol, purified water, saccharin sodium, sodium citrate, sorbitol.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antivirals

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Abacavir is a nucleoside analogue reverse transcriptase inhibitor that is metabolised intracellularly to the active moiety, carbovir 5'- triphosphate (TP) which inhibits the HIV reverse transcriptase enzyme, resulting in chain termination and interruption of the viral replication cycle.

Abacavir is a selective inhibitor of HIV-1 and HIV-2, including HIV-1 isolates with reduced susceptibility to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine.

It showed synergy *in vitro* in combination with nevirapine and zidovudine and was 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.

Pharmacokinetic properties:

Absorption:

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

There was no differences between the AUC for the tablet or solution. At a dosage of 300 mg twice daily, the mean steady state C_{max} of abacavir from tablet administration was 3,00 µg/ml, and the mean AUC over a dosing interval of 12 hours was 6,02 µg.h/ml (daily AUC of approximately 12,0 µg.h/ml). The C_{max} value for the oral solution is slightly higher than the tablet. Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore ZIAGEN can be taken with or without food.

The steady state pharmacokinetic properties of abacavir 600 mg once daily was compared to abacavir 300 mg twice daily in a crossover study in 27 HIV-infected patients. Intracellular carbovir triphosphate exposures in peripheral blood mononuclear cells were higher for abacavir 600 mg once daily with respect to $AUC_{24,ss}$ (32 %, higher), $C_{max\ 24,ss}$ (99 % higher) and trough values (18 % higher), compared to the 300 mg twice daily regimen. These data support the use of abacavir 600 mg once daily for the treatment of HIV infected patients.

Distribution:

Following intravenous administration, the apparent volume of distribution was about 0,8 ℓ/kg.

Studies in HIV infected patients have shown that abacavir enters 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 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 low to 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 was no significant medicine 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:

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.

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.

***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 therapy.

INDICATIONS:

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

CONTRA-INDICATIONS:

ZIAGEN is contra-indicated:

- in patients with known hypersensitivity to abacavir or any ingredient of the formulations
- in patients with an hereditary fructose intolerance (oral solution only)
- in patients with moderate or severe liver function impairment
- during pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity to abacavir: Refer to BOXED WARNING and SIDE EFFECTS, Description of Selected Adverse Reactions.

In clinical studies, conducted before the introduction of screening for the HLA-B*5701 allele, approximately 5 % of subjects receiving abacavir developed a hypersensitivity reaction, which in rare cases has proved fatal. Hypersensitivity is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

Patients who develop a hypersensitivity reaction must discontinue ZIAGEN and MUST not be rechallenged with ZIAGEN, or any other product containing abacavir.

Lactic acidosis/severe hepatomegaly with steatosis: Long-term use of ZIAGEN can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Symptomatic hyperlactataemia and lactic acidosis are uncommon.

Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea and tachypnoea, fatigue and weight loss.

Suspicious biochemical features include raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or 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).
- Lactate > 10 mmol/ℓ: STOP all therapy (80 % mortality).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any patient with a raised lactate level. Blood for lactate assay should be heparinised and stored on ice. After recovery, NRTIs should be avoided. Seek expert advice on medicine selection.

The above lactate values may not be applicable to paediatric patients.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of ZIAGEN alone or in combination.

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).

Mitochondrial dysfunction: Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction

include haematological disorders (anaemia, neutropenia) and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether these 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 ZIAGEN. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of ZIAGEN until diagnosis of pancreatitis is excluded.

Liver disease: Use of ZIAGEN can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of ZIAGEN 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.

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. If ZIAGEN is discontinued in patients co-

infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Fat redistribution: Redistribution/accumulation of body fat, including central obesity, dorso-cervical 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.
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. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

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 tuberculosis, cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* (*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Auto-immune disorders (such as Graves' disease, polymyositis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Opportunistic infections: Patients receiving ZIAGEN 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. Regular monitoring of viral load and CD4 counts needs to be done.

Transmission of infection: Patients should be advised that current antiretroviral therapy, including ZIAGEN, 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.

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 company sponsored clinical trials no excess risk of myocardial infarction was observed with ZIAGEN use. As a precaution the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including ZIAGEN, and action taken to minimise all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

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.

Carcinogenicity: 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 rats in the thyroid gland of males and the liver, urinary bladder, lymph nodes and the subcutis of female rats.

The majority of these tumours occurred at the highest dose levels equivalent to 24 to 32 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose equivalent to six times the expected human systemic exposure. There is no structural counterpart of 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.

Drive and operate machinery: No currently available data suggests that ZIAGEN affects the ability to drive or operate machinery

Oral Solution: ZIAGEN ORAL SOLUTION contains sorbitol and may have a laxative effect. Patients with the rare hereditary condition of sorbitol intolerance should not take ZIAGEN ORAL SOLUTION. ZIAGEN ORAL SOLUTION contains maltodextrin which may have an effect on the glycaemic control in patients with diabetes mellitus.

INTERACTIONS:

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for medicine 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 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 interactions with antiretroviral protease inhibitors and other medicines 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 %. No dose reduction of abacavir is necessary. Abacavir has no effect on the metabolism of ethanol.

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

PREGNANCY AND LACTATION:

Pregnancy:

The safety of ZIAGEN in human pregnancy has not been established. ZIAGEN should not be used during pregnancy and lactation since teratogenicity and/or foetal toxicity cannot be excluded.

Lactation:

It is expected that abacavir will be secreted into human milk. Therefore mothers on treatment with ZIAGEN should not breastfeed their babies. HIV infected women should not breastfeed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, the local official lactation and treatment guidelines should be followed when considering breastfeeding during antiretroviral therapy.

DOSAGE AND DIRECTIONS FOR USE:

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

ZIAGEN 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, ZIAGEN 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 Pharmacokinetic properties).

An oral dosing syringe is provided for accurate measurement of the prescribed dose of oral solution.

Adults, adolescents and children weighing at least 25 kg:

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

Oral Solution: The recommended dose of abacavir is 300 mg (15 ml) twice daily or 600 mg (30 ml) once daily.

Children ≥ three months and weighing less than 25 kg:

Tablets:

Children weighing 14 to < 20 kg: one-half of a scored ZIAGEN tablet twice daily or one tablet taken once daily.

Children weighing ≥ 20 kg to < 25 kg: one-half of a scored ZIAGEN tablet taken in the morning and one whole tablet taken in the evening or one and a half tablets taken once daily.

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.

Oral Solution:

The recommended dosage is 8 mg/kg twice daily or 16 mg/kg once daily up to a maximum dose of 300 mg twice daily or 600 mg once daily.

Children less than three months*:*

There are no data available on the use of ZIAGEN in this age group.

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 200 mg (10 ml) twice daily. To enable dose reduction ZIAGEN ORAL SOLUTION should be used in these patients. Pharmacokinetic and safety data on the use of ZIAGEN in patients with moderate and severe hepatic impairment are not available (see Pharmacokinetic properties). Therefore the use of ZIAGEN is contra-indicated in patients with moderate or severe hepatic impairment, unless the benefit of use outweighs the risk.

SIDE EFFECTS:

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), including isolated reports.

The adverse events reported during therapy for HIV disease with ZIAGEN were similar in adults and children.

Many of the adverse events listed occur commonly (nausea, vomiting, diarrhoea, fever, lethargy, rash) in patients with abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction. If ZIAGEN has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only

under direct medical supervision (see Special considerations following an interruption of ZIAGEN therapy in BOXED WARNING).

Clinical Trial Data

Metabolism and nutrition disorders:

Common: anorexia

Nervous system disorders:

Common: headache

Gastrointestinal disorders:

Common: nausea, vomiting, diarrhoea

General disorders and administrative site conditions:

Common: fever, lethargy, fatigue.

Paediatric population

The safety database to support ZIAGEN once daily in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects received abacavir and lamivudine either once of twice daily. 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:

Hyperlactataemia

Lactic acidosis (see WARNINGS AND SPECIAL PRECAUTIONS)

Redistribution/accumulation of body fat (see WARNINGS AND SPECIAL PRECAUTIONS). The incidence of this event is dependent on multiple factors including the particular antiretroviral treatment combination.

Gastrointestinal disorders:

Pancreatitis has been reported

Skin and subcutaneous tissue disorders:

Rash (without systemic symptoms)

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Description of Selected Adverse Reactions

Hypersensitivity (see also BOXED WARNING):

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 postmarketing surveillance. Those reported **in at least 10 % of patients** with a hypersensitivity reaction are in bold text.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however, reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin and subcutaneous tissue disorders:	**Rash** (usually maculopapular or urticarial)
Gastrointestinal disorders:	**Nausea**, **vomiting**, **diarrhoea**, **abdominal pain**, mouth ulceration

Respiratory, thoracic and mediastinal disorders:	**Dyspnoea**, **cough**, sore throat, adult respiratory distress syndrome, respiratory failure
General disorders and administrative site conditions:	**Fever**, **fatigue**, **malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Nervous system disorders:	**Headache**, paraesthesia
Blood and the lymphatic system disorders:	Lymphopenia
Hepato-biliary disorders:	**Elevated liver function tests**, hepatic failure
Musculoskeletal, connective tissue and bone disorders:	**Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Renal and urinary disorders:	Elevated creatinine, renal failure

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. **This recurrence of the HSR is usually more severe than on initial presentation, and may include life-threatening hypotension and death.** Reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

For details of clinical management in the event of a suspected abacavir HSR see BOXED WARNING.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

If overdosage occurs the patient should be monitored for evidence of toxicity (see SIDE-EFFECTS), and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

IDENTIFICATION:

ZIAGEN TABLETS: The scored tablets are biconvex, capsule-shaped, yellow tablets, engraved with 'GX 623' on both sides.

ZIAGEN ORAL SOLUTION: A clear to slightly opalescent yellowish solution with a fruity odour.

PRESENTATION:

ZIAGEN TABLETS: Available in polyvinyl chloride/foil blister packs or polyvinyl chloride/child resistant foil blister packs containing 60 tablets.

ZIAGEN ORAL SOLUTION: Supplied in high-density polyethylene bottles with child-resistant closures, containing 240 ml of oral solution. A 10 ml polypropylene oral dosing syringe and a polyethylene adaptor are also included in the pack.

STORAGE INSTRUCTIONS:

ZIAGEN TABLETS: Store at or below 30 °C.

ZIAGEN ORAL SOLUTION: Store at or below 30 °C. Discard oral solution two months after first opening.

REGISTRATION NUMBERS:

ZIAGEN TABLETS: 33/20.2.8/0464

ZIAGEN ORAL SOLUTION: 33/20.2.8/0465

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

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

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