ZIAGEN TABLETS

1. TRADE NAME OF THE MEDICINAL PRODUCT

ZIAGEN Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg of abacavir as abacavir sulfate.

3. PHARMACEUTICAL FORM

Film-coated scored tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

4.2 Posology and Method of Administration

Therapy should be initiated by a physician 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 5.2 Pharmacokinetic Properties*)

Adults, adolescents and children weighing at least 25 kg: The recommended dose of *ZIAGEN* 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: A dosing regimen according to weight bands is recommended for *ZIAGEN* scored tablets.

Tablets:

Children weighing 14 to < 20 kg: 150 mg (one-half of a scored abacavir tablet) twice daily or 300 mg (one whole tablet) taken once daily.

Children weighing ≥ 20 kg to < 25 kg: 150 mg (one-half of a scored abacavir tablet) taken in the morning and 300 mg (one whole tablet) taken in the evening or 450 mg (one and a half tablets) taken once daily.

Children weighing at least 25 kg: the adult dosage of 300 mg (one tablet) twice daily or 600 mg (two tablets) once daily should be taken.

The oral solution may be administered to children weighing less than 14 kg or those unable to swallow tablets.

Oral Solution:

The recommended dose is 8 mg/kg twice daily up to a maximum of 600 mg (30 ml of oral suspension) daily.

Children less than three months: the data available on the use of *ZIAGEN* in this age group are very limited (*see 5.2 Pharmacokinetic Properties*).

Patients changing from the twice daily dosing regimen to the once daily dosing regimen should take the recommended once daily dose (as described above) approximately 12 hours after the last twice daily dose, and then continue to take the recommended once daily dose (as described above) approximately every 24 hours. When changing back to a twice daily regimen, patients should take the recommended twice daily dose approximately 24 hours after the last once daily dose.

Renal impairment: No dosage adjustment of *ZIAGEN* is necessary in patients with renal dysfunction (*see 5.2 Pharmacokinetic Properties*).

Hepatic impairment: Abacavir is metabolised primarily by the liver. *ZIAGEN* is contra-indicated in patients with moderate or severe hepatic impairment, as the pharmacokinetics have not been studied in these patient groups (*see 5.2 Pharmacokinetic Properties*).

4.3 Contra-indications

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.

4.4 Special Warnings and Special Precautions for Use

Hypersensitivity (*see also 4.8 Undesirable Effects*)**:**

Abacavir is associated with a risk for hypersensitivity reactions (HSR) characterized by fever and/or rash with other symptoms indicating multi-organ involvement. HSR can be life-threatening, and in rare cases 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.

The following should be adhered to:

- Testing for *HLA-B*5701* status should be considered before initiating abacavir treatment and also before re-starting abacavir treatment in patients of unknown *HLA-B*5701* status who have previously tolerated abacavir.

- *ZIAGEN* is not recommended for use in patients with the *HLA-B*5701* allele, or in patients who have had a suspected abacavir HSR while taking any other medicinal product containing abacavir (e.g. *KIVEXA*^{TM}, *TRIZIVIR*^{TM}, *TRIUMEQ*^{TM}) regardless of *HLA-B*5701* status.

- Each patient should be reminded to read the Patient Alert Card 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.

- In any patient treated with *ZIAGEN*, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making.

- ***ZIAGEN* must be stopped without delay, even in the absence of the *HLA-B*5701* allele, if a HSR is suspected. Delay in stopping treatment with *ZIAGEN* after the onset of hypersensitivity may result in a life-threatening reaction.**

- Patients who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining *ZIAGEN* tablets in order to avoid restarting abacavir.

- **Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours, and may include life-threatening hypotension and death.**

- **Regardless of a patient's *HLA-B*5701* status, if therapy with any abacavir containing product has been discontinued for any reason and restarting abacavir therapy is under consideration, the reason for discontinuation must be established. If HSR cannot be ruled out, *ZIAGEN* or any other medicinal product containing abacavir (e.g. *KIVEXA, TRIZIVIR, TRIUMEQ*) must not be restarted.**

- If a hypersensitivity reaction is ruled out, patients may restart *ZIAGEN*. Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have

also experienced life-threatening reactions within hours of re-initiating abacavir therapy (*see 4.8 Description of selected adverse reactions*). Patients must be made aware that HSR can occur with reintroduction of *ZIAGEN* or any other medicinal product containing abacavir (e.g. *KIVEXA, TRIZIVIR, TRIUMEQ*) and that reintroduction of *ZIAGEN* or any other medicinal product containing abacavir (e.g. *KIVEXA, TRIZIVIR, TRIUMEQ*) should be undertaken only if medical care can be readily accessed.

Clinical Description of abacavir HSR:

Abacavir HSR has been well characterised through clinical studies and during post marketing follow-up. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, **although these reactions may occur at any time during therapy.**

Almost all HSR to abacavir include fever and/or rash as part of the syndrome.

Other signs and symptoms that have been observed as part of abacavir HSR include respiratory and gastrointestinal symptoms, **which may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis** (*see 4.8 Undesirable Effects, Description of Selected Adverse Reactions*). The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of *ZIAGEN*.

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* particularly to those with known risk factors for liver disease. However, cases have also been reported in patients with no known risk factors. Treatment with *ZIAGEN* should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Serum lipids and blood glucose: Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors. 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 jiroveci* pneumonia (often referred to as PCP). Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary. Autoimmune 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* 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 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: Several, observational, epidemiological studies have reported an association with abacavir use and the risk of myocardial infarction. Meta-analyses of randomised controlled trials have observed no excess risk of myocardial infarction with abacavir use. To date, there is no established biological mechanism to explain a potential increase in risk. In totality, the available data from observational studies and from controlled clinical trials show inconsistency and therefore the evidence for a causal relationship between abacavir treatment and the risk of myocardial infarction is inconclusive. 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).

Triple therapy: As part of a triple-drug regimen, *ZIAGEN* is generally recommended for use with antiretroviral agents from different pharmacological classes and not solely with other nucleoside/nucleotide reverse transcriptase inhibitors. This is based on results from randomised, double-blind, controlled studies in which the proportion of subjects with early virological failure was higher in the triple nucleoside groups than in groups who received regimens involving two nucleosides in combination with an agent from a different pharmacological class.

Once daily administration (abacavir 600 mg): The benefit of abacavir as a once daily regimen is mainly based on a study performed in combination with efavirenz and lamivudine, in antiretroviral-naïve adult patients.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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 CYP3A4, 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.

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 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.

4.6 Use During Pregnancy and Lactation

Pregnancy: Abacavir has been evaluated in the Antiretroviral Pregnancy Registry in over 2000 women during pregnancy and postpartum. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for abacavir compared to the background rate. However, there are no adequate and well-controlled trials in pregnant women and the safe use of *ZIAGEN* in human pregnancy has not been established. Abacavir has been associated with findings in animal reproductive studies (*see 5.3 Preclinical 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. Health experts recommend that, where possible, HIV-infected women do not breast-feed their infants in order to avoid transmission of HIV. It is therefore recommended that mothers do not breast-feed their babies while receiving treatment with *ZIAGEN*.

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable 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 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 re-start *ZIAGEN*, this should be done only under

direct medical supervision (*see 4.4 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).

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 arm.

Postmarketing Data

Metabolism and nutrition disorders

Common: hyperlactataemia.

Rare: lactic acidosis (*see 4.4 Special Warnings and Special Precautions for Use*).

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 Special Warnings and Special Precautions for Use):

Abacavir hypersensitivity reaction (HSR) has been identified as a common adverse reaction with abacavir therapy. The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in **at least 10% of patients** with a hypersensitivity reaction are in bold text.

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

Skin:	**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

Symptoms related to this HSR worsen with continued therapy and can be life-threatening and in rare instance, have been fatal.

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 *Special Warnings and Special Precautions for Use*.

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 Pharmacodynamic Properties – Clinical Experience*). Primary safety assessment in the ARROW trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing (see table below). One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator.

ARROW Study Randomization 3: Most Frequently Reported (2 or More Events Overall) of Grade 3 or 4 Adverse Events for Once- Versus Twice-Daily Dosing of Abacavir and Lamivudine by Dosing Frequency and Overall

	Twice-Daily ABC+3TC	**Once-Daily ABC+3TC**	**Total**
Total number of subjects	333	336	669
Total grade 3 or 4 AEs, n (%)	82 (25)	95 (28)	177 (26)
Hematological: computer, n (%)			
Leucopenia	2 (<1)	1 (<1)	3 (<1)
Neutropenia	15 (5)	23 (7)	38 (6)
Non-clinical anaemia	6 (2)	3 (<1)	9 (1)
Thrombocytopenia	6 (2)	10 (3)	16 (2)
Biochemical: computer, n (%)			
Hypoglycaemia	0	2 (<1)	2 (<1)
Raised ALT	5 (2)	1 (<1)	6 (<1)
Raised AST	3 (<1)	4 (1)	7 (1)
Raised bilirubin	2 (<1)	1 (<1)	3 (<1)
Raised liver enzymes	3 (<1)	5 (1)	8 (1)
Hematological: clinical report, n (%)			
Anaemia with clinical symptoms	5 (2)	7 (2)	12 (2)
Thrombocytopenia	0	2 (<1)	2 (<1)
Specific Infections, n (%)			
Measles	3 (<1)	1 (<1)	4 (<1)
Plasmodium falciparum malaria	16 (5)	16 (5)	32 (5)
Presumptive septicemia/bacteremia	3 (<1)	3 (<1)	6 (<1)
Diarrhoeal disease, n (%)			
Acute diarrhoea, not investigated	2 (<1)	2 (<1)	4 (<1)
Lower respiratory tract, n (%)			
Pneumonia, no organism identified	2 (<1)	2 (<1)	4 (<1)
Eye, n (%)			
Cataract	0	2 (<1)	2 (<1)
Undiagnosed fevers, n (%)			
Acute febrile episode	0	2 (<1)	2 (<1)
Unknown, n (%)	0	2 (<1)	2 (<1)

Dog bite			

4.9 Overdose

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 overdosage occurs, the patient should be monitored for evidence of toxicity (*see 4.8 Undesirable Effects*), and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

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

In a study of 20 HIV-infected patients receiving *ZIAGEN* 300 mg twice daily, with only one 300 mg dose taken prior to the 24 hour sampling period, 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 *ZIAGEN* 600 mg once daily. These data support the use of *ZIAGEN* 600 mg once daily for the treatment of HIV-infected patients. Additionally, the efficacy of *ZIAGEN* 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 IC_{50} over wild-type virus, which may be a clinically relevant level.

Isolates resistant to abacavir may also show reduced sensitivity to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. Cross resistance between abacavir and protease inhibitors or non nucleoside reverse transcriptase inhibitors is unlikely. Reduced susceptibility to abacavir has been demonstrated in clinical isolates of 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.

Clinical Experience: 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 and lamivudine was investigated in a multicentre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. They were randomised to receive either *ZIAGEN* 600 mg once daily or 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. Patients were stratified at baseline based on plasma HIV-1 RNA less than or equal to 100,000 copies/ml or greater than 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 less than 50 copies/ml at Week 48 ITT-Exposed Population

Populations	ABC once/day + 3TC + EFV (N = 384)	ABC twice/day + 3TC + EFV (N = 386)	Point Estimate	95% CI*
Stratified			-1.7	-8.4, 4.9
Sub-group by baseline RNA				
≤100,000 copies/ml	141/217 (65%)	145/217 (67%)	-1.8	-10.8, 7.1
>100,000 copies/ml	112/167 (67%)	116/169 (69%)	-1.6	-11.6, 8.4
Total population	253/384 (66%)	261/386 (68%)		

* Confidence interval

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 was similar in the two treatment groups.

Genotypic analysis was attempted for all subjects with virologic failure (confirmed HIV RNA greater than 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 genotyping was restricted to samples with plasma HIV-1 RNA greater than 500 copies/ml. These factors resulted in a small sample size. In this small sample size, there was a trend toward a higher rate of NRTI-associated mutations in the once daily versus the twice daily abacavir regimens. No firm conclusion could be drawn due to the limited data derived from this study. Genotypic (n=38) and phenotypic analyses (n=35) of virologic failure isolates from this study showed that the abacavir- and lamivudine-associated resistance mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir/lamivudine once daily (56%,

10/18) and twice daily (40%, 8/20). L74V, Y115F and K65R were the other RT mutations observed in the study.

Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a ≥ 2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13). Fifty-six percent (10/18) of the virologic failure isolates in the once-daily abacavir group compared to 41% (7/17) of the failure isolates in the twice-daily abacavir group had a ≥ 2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range 0.79 to >116) and 1.1 (range 0.68 to >116) in the once-daily and twice-daily abacavir arm, respectively. Long term data with abacavir used as a once daily regimen (beyond 48 weeks) are currently limited.

A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. Of note, from this study clinical data were not available for children under one year old. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily N (%)	**Once Daily N (%)**
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/mL	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/mL	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/mL	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

The abacavir/lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/mL, <400c/mL, <1000c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

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 ≤ 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 a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/mL at Week 48. No safety concerns were observed in these subjects.

In therapy-experienced patients, the degree of benefit from the addition of abacavir 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 5.2 Pharmacokinetic Properties*), 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.

5.2 Pharmacokinetic Properties

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 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. After a 600 mg abacavir tablet dose, the mean abacavir C_{max} was approximately 4.26 μg/ml and the mean AUC was 11.95 μg.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.

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 characteristics of the active ingredient and the *in vitro* dissolution behaviour of abacavir tablets in water, 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.

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 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 (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 300 mg 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.

Special patient 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 200 mg 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: According to clinical trials performed in children, abacavir is rapidly and well absorbed from oral solution and tablet formulations administered to children. Plasma abacavir exposure has been shown to be the same for both formulations when administered at the same dose. Children receiving abacavir oral solution according to the recommended dosage regimen achieve plasma abacavir exposure similar to adults. Children receiving abacavir oral tablets according to the recommended dosage regimen achieve higher plasma abacavir exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation.

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

Pharmacokinetic data were derived from 3 pharmacokinetic studies (PENTA 13, PENTA 15 and ARROW PK substudy) enrolling children under 12 years of age. The data are displayed in the table below:

Summary of Steady-State Plasma Abacavir AUC (0-24) (µg.h/mL) and Statistical Comparisons for Once and Twice-Daily Oral Administration Across Studies

Study	Age Group	Abacavir 16 mg/kg Once-Daily Dosing Geometric Mean (95% CI)	Abacavir 8 mg/kg Twice-Daily Dosing Geometric Mean (95% CI)	Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% CI)
ARROW PK Substudy Part 1	3 to 12 years (N=36)	15.3 (13.3-17.5)	15.6 (13.7-17.8)	0.98 (0.89, 1.08)
PENTA 13	2 to 12 years (N=14)	13.4 (11.8-15.2)	9.91 (8.3-11.9)	1.35 (1.19-1.54)
PENTA 15	3 to 36 months (N=18)	11.6 (9.89-13.5)	10.9 (8.9-13.2)	1.07 (0.92-1.23)

In PENTA 15 study, the geometric mean plasma abacavir AUC(0-24) (95% CI) of the four subjects under 12 months of age who switch from a twice daily to a once daily regimen (see section 5.1) are 15.9 (8.86, 28.5) µg.h/mL in the once-daily dosing and 12.7 (6.52, 24.6) µg.h/mL in the twice-daily dosing.

Across the three studies (PENTA 13, PENTA 15 and ARROW PK substudy), the mean C_{max} was approximately 1.6- to 2.3-fold higher with abacavir once-daily dosing compared with twice-daily dosing.

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.

5.3 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 330 mg/kg/day in mice and 600 mg/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 110 mg/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 foetuses occurred only in rats at maternally toxic doses of 500 mg/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 160 mg/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 500 mg/kg of abacavir had no effect on male or female fertility.

Special Precautions for Storage

Do not store above 30°C.

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