**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Ziagen 300 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of abacavir (as sulfate).

For the full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablets)

The scored tablets are yellow, biconvex, capsule shaped and are engraved with ‘GX 623’ on both sides.

The tablet can be divided into equal halves.

## 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, adolescents and children (see sections 4.4 and 5.1).

The demonstration of the benefit of Ziagen is mainly based on results of studies performed with a twice daily regimen, in treatment-naïve adult patients on combination therapy (see section 5.1).

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin(see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele

### 4.2 Posology and method of administration

Ziagen should be prescribed by physicians 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.

Ziagen is also available as an oral solution for use in children over three months of age and weighing less than 14 kg and for those patients for whom the tablets are inappropriate.

Alternatively, for patients who are unable to swallow tablets, the tablet(s) may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

*Adults, adolescents and children (weighing at least 25 kg):*

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 (see sections 4.4 and 5.1).

*Children (weighing less than 25 kg):*

Dosing according to weight bands is recommended for Ziagen tablets.

*Children weighing ≥ 20 kg to < 25 kg*: The recommended dose is 450 mg daily. This may be administered as either one 150 mg (one half of a 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 14 to < 20 kg:* The recommended dose is 300 mg daily. This may be administered as either 150 mg (one half of a tablet) twice daily or 300 mg (one whole tablet) once daily.

*Children less than three months of age:* The clinical experience in children aged less than three months is limited and are insufficient to propose specific dosage recommendations (see section 5.2).

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.

*Special populations*

*Renal impairment*
No dosage adjustment of Ziagen is necessary in patients with renal dysfunction. However, Ziagen is not recommended for patients with end-stage renal disease (see section 5.2).

*Hepatic impairment*
Abacavir is primarily metabolised by the liver. No definitive dose recommendation can be made in patients with mild hepatic impairment (Child-Pugh score 5-6). In patients with moderate or severe hepatic impairment, no clinical data are available, therefore the use of abacavir is not recommended unless judged necessary. If abacavir is used in patients with mild hepatic impairment, then close monitoring is required, including monitoring of abacavir plasma levels if feasible (see sections 4.4 and 5.2).

*Elderly*
No pharmacokinetic data are currently available in patients over 65 years of age.

## 4.3 Contraindications

Hypersensitivity to abacavir or to any of the excipients listed in section 6.1. See sections 4.4 and 4.8.

## 4.4 Special warnings and precautions for use

Hypersensitivity reactions (see also section 4.8)

Abacavir is associated with a risk for hypersensitivity reactions (HSR) (see section4.8) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.
The risk for abacavir HSR to occur is high 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.

Therefore the following should be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- Ziagen should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen. (e.g. Kivexa, Trizivir, Triumeq)
- **Ziagen must be stopped without delay**, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Ziagen after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with Ziagen for reasons of a suspected HSR, **Ziagen or any other medicinal product containing abacavir** (e.g. Kivexa, Trizivir, Triumeq) **must never be re-initiated**.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.
- In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining Ziagen tablets

*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. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms **may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.**

The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

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 Section 4.8 Description of selected adverse reactions). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside

analogues ; these have predominantly concerned treatment with regimens containing zidovudine.The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleotide and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain.

Triple nucleoside therapy

In patients with high viral load (>100,000 copies/ml) the choice of a triple combination with abacavir, lamivudine and zidovudine needs special consideration (see section 5.1).

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

Liver disease

The safety and efficacy of Ziagen has not been established in patients with significant underlying liver disorders. Ziagen is not recommended in patients with moderate or severe hepatic impairment (see sections 4.2 and 5.2 ).
Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with chronic hepatitis B or C virus

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

Renal disease

Ziagen should not be administered to patients with end-stage renal disease (see section 5.2).
Excipients

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving 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

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Myocardial Infarction

Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Ziagen, action should be taken to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

## 4.5 Interaction with other medicinal products and other forms of interaction

The potential for P450 mediated interactions with other medicinal products involving abacavir is low. In vitro studies have shown that abacavir has potential to inhibit cytochrome P450 1A1 (CYP1A1). P450 does not play a major role in the metabolism of abacavir, and abacavir shows limited potential to inhibit metabolism mediated by CYP 3A4. Abacavir has also been shown *in vitro* not to inhibit, CYP2C9 or CYP2D6 enzymes at clinically relevant concentrations. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for interactions with antiretroviral PIs and other medicinal products metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

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

*Ethanol:* the metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%. These findings are not considered clinically significant. 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%. The induction of drug metabolising enzymes cannot therefore be excluded. Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms indicating under dosing, as occasionally methadone re-titration may be required.

*Retinoids:* retinoid compounds are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, both animal data as well as clinical experience in pregnant women should be taken into account. Animal studies have shown toxicity to the developing embryo and foetus in rats, but not in rabbits (see section 5.3). Abacavir has been shown to be carcinogenic in animal models (see section 5.3). Clinical relevance in human of these data is unknown. Placental transfer of abacavir and/or its related metabolites has been shown to occur in human.

In pregnant women, more than 800 outcomes after first trimester exposure and more than 1000 outcomes after second and third trimester exposure indicate no malformative and foetal/neonatal effect of abacavir. The malformative risk is unlikely in humans based on those data.

*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 (see section 4.4).

Breast-feeding

Abacavir and its metabolites are excreted into the milk of lactating rats. Abacavir is also excreted into human milk. There are no data available on the safety of abacavir when administered to babies less than three months old. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

Studies in animals showed that abacavir had no effect on fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

## 4.8 Undesirable effects

For many adverse reactions reported, it is unclear whether they are related to Ziagen, to the wide range of medicinal products used in the management of HIV infection or as a result of the disease process. Many of the adverse reactions listed below 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 (see section 4.4). Very rarely cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicinal products containing abacavir should be permanently discontinued.

Many of the adverse reactions have not been treatment limiting. The following convention has been used for their classification: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to <1/1,000) very rare (<1/10,000).

Metabolism and nutrition disorders
*Common:* anorexia
*Very rare*: lactic acidosis

Nervous system disorders
*Common*: headache

Gastrointestinal disorders
*Common*: nausea, vomiting, diarrhoea
*Rare:* pancreatitis

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 conditions
*Common*: fever, lethargy, fatigue

Description of Selected Adverse Reactions

*Abacavir hypersensitivity reactions*
The signs and symptoms of this HSR 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, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis |
| *Neurological/Psychiatry* | **Headache**, paraesthesia |
| *Haematological* | Lymphopenia |
| *Liver/pancreas* | **Elevated liver function tests,** hepatitis, 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. Similar 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).

*Metabolic parameters*
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

*Immune reactivation syndrome*
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART) an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

*Osteonecrosis*
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

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

Paediatric population

1206 HIV-infected paediatric patients aged 3 months to 17 years were enrolled in the ARROW Trial (COL105677), 669 of whom received abacavir and lamivudine either once or twice daily (see section 5.1). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Single doses up to 1200 mg and daily doses up to 1800 mg of Ziagen have been administered to patients in clinical studies. No additional adverse reactions to those reported for normal doses were reported. The effects of higher doses are not known. If overdose occurs the patient should be monitored for evidence of toxicity (see section 4.8), 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 reverse transcriptase inhibitors, ATC Code: J05AF06

Mechanism of action

Abacavir is a NRTI. It is a potent selective inhibitor of HIV-1 and HIV-2. 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 antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Resistance

*In vitro resistance*

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*, requiring multiple mutations for a clinically relevant increase in $EC_{50}$ over wild-type virus.

*In vivo resistance (Therapy naïve patients)*

Isolates from most patients experiencing virological failure with a regimen containing abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline (45%) or only M184V or M184I selection (45%). The overall selection frequency for M184V or M184I was high (54%), and less common was the selection of L74V (5%), K65R (1%) and Y115F (1%). The inclusion of zidovudine in the regimen has been found to reduce the frequency of L74V and K65R selection in the presence of abacavir (with zidovudine: 0/40, without zidovudine: 15/192, 8%).

| Therapy | Abacavir + Combivir[1] | Abacavir + lamivudine + NNRTI | Abacavir + lamivudine + PI (or PI/ritonavir) | Total |
|---|---|---|---|---|
| **Number of Subjects** | 282 | 1094 | 909 | 2285 |
| **Number of Virological Failures** | 43 | 90 | 158 | 291 |
| **Number of On-Therapy Genotypes** | 40 (100%) | 51 (100%)[2] | 141 (100%) | 232 (100%) |
| **K65R** | 0 | 1 (2%) | 2 (1%) | 3 (1%) |
| **L74V** | 0 | 9 (18%) | 3 (2%) | 12 (5%) |
| **Y115F** | 0 | 2 (4%) | 0 | 2 (1%) |
| **M184V/I** | 34 (85%) | 22 (43%) | 70 (50%) | 126 (54%) |
| **TAMs[3]** | 3 (8%) | 2 (4%) | 4 (3%) | 9 (4%) |

1.Combivir is a fixed dose combination of lamivudine and zidovudine
2.Includes three non-virological failures and four unconfirmed virological failures.
3. Number of subjects with ≥1 Thymidine Analogue Mutations (TAMs).

TAMs might be selected when thymidine analogs are associated with abacavir. In a meta-analysis of six clinical trials, TAMs were not selected by regimens containing abacavir without zidovudine (0/127), but were selected by regimens containing abacavir and the thymidine analogue zidovudine (22/86, 26%).

*In vivo resistance (Therapy experienced patients)*

Clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. In a meta-analysis of five clinical trials where abacavir was added to intensify therapy, of 166 subjects, 123 (74%) had M184V/I, 50 (30%) had T215Y/F, 45 (27%) had M41L, 30 (18%) had K70R and 25 (15%) had D67N. K65R was absent and L74V and Y115F were uncommon (≤3%). Logistic regression modelling of the predictive value for genotype (adjusted for baseline plasma HIV-1 RNA [vRNA], CD4+ cell count, number and duration of prior antiretroviral therapies), showed that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at Week 4 ($p=0.015$) or 4 or more mutations at median Week 24 ($p\leq0.012$). In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, cause a high level of resistance to abacavir.

| Baseline Reverse Transcriptase Mutation | Week 4 (n = 166) | | |
|---|---|---|---|
| | n | Median Change vRNA ($log_{10}$ c/ml) | Percent with <400 copies/ml vRNA |
| **None** | 15 | -0.96 | 40% |
| **M184V alone** | 75 | -0.74 | 64% |
| **Any one NRTI mutation** | 82 | -0.72 | 65% |
| **Any two NRTI-associated mutations** | 22 | -0.82 | 32% |
| **Any three NRTI-associated mutations** | 19 | -0.30 | 5% |
| **Four or more NRTI-associated mutations** | 28 | -0.07 | 11% |

*Phenotypic resistance and cross-resistance*

Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple TAMs. Phenotypic cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir maintain their antiretroviral activities against such HIV-1 variants. The presence of M184V with K65R does give rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. The presence of M184V with Y115F gives rise to cross-resistance between abacavir and lamivudine. Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

Cross-resistance between abacavir and antiretrovirals from other classes (e.g. PIs or NNRTIs) is unlikely.

Clinical efficacy and safety

The demonstration of the benefit of Ziagen is mainly based on results of studies performed in adult treatment-naïve patients using a regimen of Ziagen 300 mg twice daily in combination with zidovudine and lamivudine.

*Twice daily (300 mg) administration:*

- *Therapy naïve adults*

In adults treated with abacavir in combination with lamivudine and zidovudine the proportion of patients with undetectable viral load (<400 copies/ml) was approximately 70% (intention to treat analysis at 48 weeks) with corresponding rise in CD4 cells.

One randomised, double blind, placebo controlled clinical study in adults has compared the combination of abacavir, lamivudine and zidovudine to the combination of indinavir, lamivudine and zidovudine. Due to the high proportion of premature discontinuation (42% of patients discontinued randomised treatment by week 48), no definitive conclusion can be drawn regarding the equivalence between the treatment regimens at week 48. Although a similar antiviral effect was observed between

the abacavir and indinavir containing regimens in terms of proportion of patients with undetectable viral load (≤400 copies/ml; intention to treat analysis (ITT), 47% versus 49%; as treated analysis (AT), 86% versus 94% for abacavir and indinavir combinations respectively), results favoured the indinavir combination, particularly in the subset of patients with high viral load (>100,000 copies/ml at baseline; ITT, 46% versus 55%; AT, 84% versus 93% for abacavir and indinavir respectively).

In a multicentre, double-blind, controlled study (CNA30024), 654 HIV-infected, antiretroviral therapy-naïve patients were randomised to receive either abacavir 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily. The duration of double-blind treatment was at least 48 weeks. In the intent-to-treat (ITT) population, 70% of patients in the abacavir group, compared to 69% of patients in the zidovudine group, achieved a virologic response of plasma HIV-1 RNA ≤50 copies/ml by Week 48 (point estimate for treatment difference: 0.8, 95% CI -6.3, 7.9). In the as treated (AT) analysis the difference between both treatment arms was more noticeable (88% of patients in the abacavir group, compared to 95% of patients in the zidovudine group (point estimate for treatment difference: -6.8, 95% CI -11.8; -1.7). However, both analyses were compatible with a conclusion of non-inferiority between both treatment arms.

ACTG5095 was a randomised (1:1:1), double-blind, placebo-controlled trial performed in 1147 antiretroviral naïve HIV-1 infected adults, comparing 3 regimens: zidovudine (ZDV), lamivudine (3TC), abacavir (ABC), efavirenz (EFV) vs ZDV/3TC/EFV vs ZDV/3TC/ABC. After a median follow-up of 32 weeks, the tritherapy with the three nucleosides ZDV/3TC/ABC was shown to be virologically inferior to the two other arms regardless of baseline viral load (< or > 100 000 copies/ml) with 26% of subjects on the ZDV/3TC/ABC arm, 16% on the ZDV/3TC/EFV arm and 13% on the 4 drug arm categorised as having virological failure (HIV RNA >200 copies/ml). At week 48 the proportion of subjects with HIV RNA <50 copies/ml were 63%, 80% and 86% for the ZDV/3TC/ABC, ZDV/3TC/EFV and ZDV/3TC/ABC/EFV arms, respectively. The study Data Safety Monitoring Board stopped the ZDV/3TC/ABC arm at this time based on the higher proportion of patients with virologic failure. The remaining arms were continued in a blinded fashion. After a median follow-up of 144 weeks, 25% of subjects on the ZDV/3TC/ABC/EFV arm and 26% on the ZDV/3TC/EFV arm were categorised as having virological failure. There was no significant difference in the time to first virologic failure (p=0.73, log-rank test) between the 2 arms. In this study, addition of ABC to ZDV/3TC/EFV did not significantly improve efficacy.

| | | ZDV/3TC/ABC | ZDV/3TC/EFV | ZDV/3TC/ABC/EFV |
|---|---|---|---|---|
| Virologic failure (HIV RNA >200 copies/ml) | 32 weeks | 26% | 16% | 13% |
| | 144 weeks | - | 26% | 25% |
| Virologic success (48 weeks HIV RNA < 50 copies/ml) | | 63% | 80% | 86% |

- *Therapy experienced adults*

In adults moderately exposed to antiretroviral therapy the addition of abacavir to combination antiretroviral therapy provided modest benefits in reducing viral load (median change 0.44 $\log_{10}$ copies/ml at 16 weeks).

In heavily NRTI pretreated patients the efficacy of abacavir is very low. The degree of benefit as part of a new combination regimen will depend on the nature and duration of prior therapy which may have selected for HIV-1 variants with cross-resistance to abacavir.

*Once daily (600 mg) administration:*

- *Therapy naïve adults*

The once daily regimen of abacavir is supported by a 48 weeks multi-centre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. These were primarily asymptomatic HIV infected patients - Centre for Disease Control and Prevention (CDC) stage A. They were randomised to receive either abacavir 600 mg once daily or 300 mg twice daily, in combination with efavirenz and lamivudine given once daily. Similar clinical success (point estimate for treatment difference -1.7, 95% CI -8.4, 4.9) was observed for both regimens. From these results, it can be concluded with 95% confidence that the true difference is no greater than 8.4% in favour of the twice daily regimen. This potential difference is sufficiently small to draw an overall conclusion of non-inferiority of abacavir once daily over abacavir twice daily.

There was a low, similar overall incidence of virologic failure (viral load >50 copies/ml) in both the once and twice daily treatment groups (10% and 8% respectively). In the small sample size for genotypic analysis, 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. Long term data with abacavir used as a once daily regimen (beyond 48 weeks) are currently limited.

- *Therapy experienced adults*

In study CAL30001, 182 treatment-experienced patients with virologic failure were randomised and received treatment with either the fixed-dose combination of abacavir/lamivudine (FDC) once daily or abacavir 300 mg twice daily plus lamivudine 300 mg once daily, both in combination with tenofovir and a PI or an NNRTI for 48 weeks. Results indicate that the FDC group was non-inferior to the abacavir twice daily group, based on similar reductions in HIV-1 RNA as measured by average area under the curve minus baseline (AAUCMB, -1.65 $\log_{10}$ copies/ml versus -1.83 $\log_{10}$ copies/ml respectively, 95% CI -0.13, 0.38). Proportions with HIV-1 RNA < 50 copies/ml (50% versus 47%) and < 400 copies/ml (54% versus 57%) were also similar in each group (ITT population). However, as there were only moderately experienced patients included in this study with an imbalance in baseline viral load between the arms, these results should be interpreted with caution.

In study ESS30008, 260 patients with virologic suppression on a first line therapy regimen containing abacavir 300 mg plus lamivudine 150 mg, both given twice daily and a PI or NNRTI, were randomised to continue this regimen or switch to abacavir/lamivudine FDC plus a PI or NNRTI for 48 weeks.

Results indicate that the FDC group was associated with a similar virologic outcome (non-inferior) compared to the abacavir plus lamivudine group, based on proportions of subjects with HIV-1 RNA < 50 copies/ml (90% and 85% respectively, 95% CI -2.7, 13.5).

*Additional information:*

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

Abacavir penetrates the cerebrospinal fluid (CSF) (see section 5.2), 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.

*Paediatric population:*

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 separate study comparing the unblinded NRTI combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA ≤400 copies/ml at 48 weeks, compared with those treated with lamivudine and zidovudine (47%)[ p=0.09, intention to treat analysis]. Similarly, greater proportions of children treated with the abacavir containing combinations had HIV-1 RNA ≤50 copies/ml at 48 weeks (53%, 42% and 28% respectively, p=0.07).

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.

## 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.

At therapeutic dosages a dosage of 300 mg twice daily, the mean (CV) steady state $C_{max}$ and $C_{min}$ of abacavir are approximately 3.00 μg/ml (30%) and 0.01 μg/ml (99%), respectively. The mean (CV) AUC over a dosing interval of 12 hours was 6.02 μg.h/ml (29%), equivalent to a 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 (CV) abacavir $C_{max}$ was approximately 4.26 μg/ml (28%) and the mean (CV) $AUC_{\infty}$ was 11.95 μg.h/ml (21%).

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 data, assuming that the patient crushes and transfers 100% of the tablet and ingests immediately.

Distribution

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

Studies in HIV infected patients have shown good penetration of abacavir into the CSF, with a CSF to plasma AUC ratio of between 30 to 44%. The observed values of the peak concentrations are 9 fold greater than the $IC_{50}$ of abacavir of 0.08 μg/ml or 0.26 μM when abacavir is given at 600 mg twice daily**.**

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 interactions with other medicinal products through plasma protein binding displacement.

Biotransformation

Abacavir is primarily metabolised by the liver with approximately 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. The metabolites are excreted in the urine.

Elimination

The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant accumulation of abacavir. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine. The remainder is eliminated in the faeces.

Intracellular pharmacokinetics

In a study of 20 HIV-infected patients receiving abacavir 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. In a crossover study in 27 HIV-infected patients, intracellular carbovir-TP exposures were higher for the abacavir 600 mg once daily regimen ($AUC_{24,ss}$ + 32 %, $C_{max24,ss}$ + 99 % and $C_{trough}$ + 18 %) compared to the 300 mg twice daily regimen. Overall, these data support the use of abacavir 600 mg once daily for the treatment of HIV infected patients. Additionally, the efficacy and safety of abacavir given once daily has been demonstrated in a pivotal clinical study (CNA30021- See section 5.1 Clinical experience).

Special patient populations

*Hepatic impairment*
Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose ; the median (range) AUC value was 24.1 (10.4 to 54.8) ug.h/ml. The results showed that there was a mean (90%CI) increase of 1.89 fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No definitive recommendation on dosage reduction is possible in patients with mild hepatic impairment due to the substantial variability of abacavir exposure.
Abacavir is not recommended in patients with moderate or severe hepatic impairment.

*Renal impairment*

Abacavir is primarily metabolised by the liver with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment. Based on limited experience Ziagen should be avoided in patients with end-stage renal disease.

*Paediatric population*

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 Stead-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% Cl) | Abacavir 8 mg/kg Twice-Daily Dosing Geometric Mean (95% Cl) | Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% Cl) |
|---|---|---|---|---|
| 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.

*Elderly*

The pharmacokinetics of abacavir has not been studied in patients over 65 years of age.

### 5.3 Preclinical safety data

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 has a weak potential to cause chromosomal damage 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 rats in the thyroid gland of males and the liver, urinary bladder, lymph nodes and the subcutis of females.

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. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

In pre-clinical toxicology studies, abacavir treatment was shown to increase liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, autoinduction of abacavir metabolism or induction of the metabolism of other medicinal products hepatically metabolised has not been observed in man.

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.

In reproductive toxicity studies, embryo and foetal toxicity have been observed in rats but not in rabbits. These findings included decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and still births. No conclusion can be drawn with regard to the teratogenic potential of abacavir because of this embryo-foetal toxicity.

A fertility study in the rat has shown that abacavir had no effect on male or female fertility.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet Core
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate
Colloidal anhydrous silica

Tablet Coating
Triacetin
Methylhydroxypropylcellulose
Titanium dioxide
Polysorbate 80
Iron oxide yellow

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf-life

3 years

### 6.4 Special precautions for storage

Do not store above 30°C

### 6.5 Nature and contents of container

Child-resistant foil blister packs (polyvinyl chloride/aluminium/paper) containing 60 tablets.

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/112/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 July 1999

Date of latest renewal: 21 March 2014

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

## 1. NAME OF THE MEDICINAL PRODUCT

Ziagen 20 mg/ml oral solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 20 mg of abacavir (as sulfate).

Excipients with known effect:

Sorbitol (E420) 340 mg/ml
Methyl parahydroxybenzoate (E218) 1.5 mg/ml
Propyl parahydroxybenzoate (E216) 0.18 mg/ml

For the full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral solution

The oral solution is clear to slightly opalescent yellowish, aqueous solution which may turn into a brown colour over time

## 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, adolescents and children (see sections 4.4 and 5.1).

The demonstration of the benefit of Ziagen is mainly based on results of studies performed in treatment-naïve adult patients on combination therapy with a twice daily regimen (see section 5.1).

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin(see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

### 4.2 Posology and method of administration

Ziagen should be prescribed by physicians experienced in the management of HIV infection.

Ziagen can be taken with or without food.

Ziagen is also available as a tablet formulation.

*Adults, adolescents and children (weighing at least 25 kg):*

The recommended dose of Ziagen is 600 mg daily (30 ml). This may be administered as either 300 mg (15 ml) twice daily or 600 mg (30 ml) once daily (see sections 4.4 and 5.1).

*Children (weighing less than 25 kg):*

*Children from one year of age*: The recommended dose is 8 mg/kg twice daily or 16 mg/kg once daily, up to a maximum total daily dose of 600 mg (30 ml).

*Children from three months to one year of age*: The recommended dose is 8 mg/kg twice daily. If a twice daily regimen is not feasible, a once daily regimen (16 mg/kg/day) could be considered. It should be taken into account that data for the once daily regimen are very limited in this population (see sections 5.1 and 5.2).

*Children less than three months of age:* the experience in children aged less than three months is limited (see section 5.2).

Patients changing from the twice daily dosing regimen to the once daily dosing regimen should take the recomended once daily dose (as described above) approximately 12 hours after the last twice daily dose, and then continue to take the recomended 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.

*Special populations*

*Renal impairment*
No dosage adjustment of Ziagen is necessary in patients with renal dysfunction. However, Ziagen is not recommended for patients with end-stage renal disease (see section 5.2).

*Hepatic impairment*
Abacavir is primarily metabolised by the liver. No definitive dose recommendation can be made in patients with mild hepatic impairment (Child-Pugh score 5-6). In patients with moderate or severe hepatic impairment, no clinical data are available, therefore the use of abacavir is not recommended unless judged necessary. If abacavir is used in patients with mild hepatic impairment, then close monitoring is required, including monitoring of abacavir plasma levels if feasible (see sections 4.4 and 5.2).

*Elderly*
No pharmacokinetic data are currently available in patients over 65 years of age.

## 4.3 Contraindications

Hypersensitivity to abacavir or to any of the excipients listed in section 6.1. See sections 4.4 and 4.8.

## 4.4 Special warnings and precautions for use

Hypersensitivity reactions (see also section 4.8):

Abacavir is associated with a risk for hypersensitivity reactions (HSR) (see section4.8) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for abacavir HSR to occur is high 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.

Therefore the following should be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- Ziagen should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen. (e.g. Kivexa, Trizivir, Triumeq)
- **Ziagen must be stopped without delay**, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Ziagen after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with Ziagen for reasons of a suspected HSR, **Ziagen or any other medicinal product containing abacavir** (e.g. Kivexa, Trizivir, Triumeq) **must never be re-initiated**.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.
- In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining Ziagen tablets

- *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. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms may lead **to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis** .

The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

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 Section 4.8 Description of selected adverse reactions). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues ; these have predominantly concerned treatment with regimens containing zidovudine.The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset

neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleotide and nucleotide analogues, who presents with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain.

Triple nucleoside therapy

In patients with high viral load (>100,000 copies/ml) the choice of a triple combination with abacavir, lamivudine and zidovudine needs special consideration (see section 5.1).

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

Liver disease

The safety and efficacy of Ziagen has not been established in patients with significant underlying liver disorders. Ziagen is not recommended in patients with moderate or severe hepatic impairment (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with chronic hepatitis B or C virus

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

Renal disease

Ziagen should not be administered to patients with end-stage renal disease (see section 5.2).

Excipients

Ziagen oral solution contains 340 mg/ml of sorbitol. When taken according to the dosage recommendations each 15 ml dose contains approximately 5 g of sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol can have a mild laxative effect. The calorific value of sorbitol is 2.6 kcal/g.

Ziagen oral solution also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving 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

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Myocardial Infarction

Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Ziagen, action should be taken to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

## 4.5 Interaction with other medicinal products and other forms of interaction

The potential for P450 mediated interactions with other medicinal products involving abacavir is low. In vitro studies have shown that abacavir has potential to inhibit cytochrome P450 1A1 (CYP1A1). P450 does not play a major role in the metabolism of abacavir, and abacavir shows limited potential to inhibit metabolism mediated by CYP 3A4. Abacavir has also been shown *in vitro* not to inhibit CYP2C9 or CYP2D6 enzymes at clinically relevant concentrations. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for interactions with antiretroviral PIs and other medicinal products metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

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

*Ethanol:* the metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%. These findings are not considered clinically significant. 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%. The induction of drug metabolising enzymes cannot therefore be excluded. Patients being treated with methadone and abacavir should be monitored for evidence of withdrawal symptoms indicating under dosing, as occasionally methadone re-titration may be required.

*Retinoids:* retinoid compounds are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, both animal data as well as clinical experience in pregnant women should be taken into account.

Animal studies have shown toxicity to the developing embryo and foetus in rats, but not in rabbits (see section 5.3). Abacavir has been shown to be carcinogenic in animal models (see section 5.3). Clinical relevance in human of these data is unknown. Placental transfer of abacavir and/or its related metabolites has been shown to occur in human.

In pregnant women, more than 800 outcomes after first trimester exposure and more than 1000 outcomes after second and third trimester exposure indicate no malformative and foetal /neonatal effect of abacavir. The malformative risk is unlikely in humans based on those data.

*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 (see section 4.4).

Breast-feeding

Abacavir and its metabolites are excreted into the milk of lactating rats. Abacavir is also excreted into human milk. There are no data available on the safety of abacavir when administered to babies less than three months old. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

Studies in animals showed that abacavir had no effect on fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

## 4.8 Undesirable effects

For many adverse reactions reported, it is unclear whether they are related to Ziagen, to the wide range of medicinal products used in the management of HIV infection or as a result of the disease process.
Many of the adverse reactions listed below 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 (see section 4.4). Very rarely cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicinal products containing abacavir should be permanently discontinued.

Many of the adverse reactions have not been treatment limiting. The following convention has been used for their classification: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to <1/1,000) very rare (<1/10,000).

Metabolism and nutrition disorders
*Common:* anorexia
*Very rare:* lactic acidosis

Nervous system disorders
*Common:* headache

Gastrointestinal disorders
*Common:* nausea, vomiting, diarrhoea
*Rare:* pancreatitis

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 conditions
*Common:* fever, lethargy, fatigue

Description of Selected Adverse Reactions

*Abacavir hypersensitivity reactions*
The signs and symptoms of this HSR 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, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis |
| *Neurological/Psychiatry* | **Headache**, paraesthesia |
| *Haematological* | Lymphopenia |
| *Liver/pancreas* | **Elevated liver function tests,** hepatitis, 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. Similar 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).

*Metabolic parameters*
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

*Immune reactivation syndrome*
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART) an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

*Osteonecrosis*

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Changes in laboratory chemistries

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

Paediatric population

1206 HIV-infected paediatric patients aged 3 months to 17 years were enrolled in the ARROW Trial (COL105677), 669 of whom received abacavir and lamivudine either once or twice daily (see section 5.1). No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

Single doses up to 1200 mg and daily doses up to 1800 mg of Ziagen have been administered to patients in clinical studies. No additional adverse reactions to those reported for normal doses were reported. The effects of higher doses are not known. If overdose occurs the patient should be monitored for evidence of toxicity (see section 4.8), 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 reverse transcriptase inhibitors, ATC Code: J05AF06

Mechanism of action

Abacavir is a NRTI. It is a potent selective inhibitor of HIV-1 and HIV-2. 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 antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Resistance

*In vitro resistance*

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,* requiring multiple mutations for a clinically relevant increase in $EC_{50}$ over wild-type virus.

*In vivo resistance (Therapy naïve patients)*

Isolates from most patients experiencing virological failure with a regimen containing abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline (45%) or only M184V or M184I selection (45%). The overall selection frequency for M184V or M184I was high (54%), and less common was the selection of L74V (5%), K65R (1%) and Y115F (1%). The inclusion of zidovudine in the regimen has been found to reduce the frequency of L74V and K65R selection in the presence of abacavir (with zidovudine: 0/40, without zidovudine: 15/192, 8%).

| **Therapy** | **Abacavir + Combivir[1]** | **Abacavir + lamivudine + NNRTI** | **Abacavir + lamivudine + PI (or PI/ritonavir)** | **Total** |
|---|---|---|---|---|
| **Number of Subjects** | 282 | 1094 | 909 | 2285 |
| **Number of Virological Failures** | 43 | 90 | 158 | 291 |
| **Number of On-Therapy Genotypes** | 40 (100%) | 51 (100%)[2] | 141 (100%) | 232 (100%) |
| **K65R** | 0 | 1 (2%) | 2 (1%) | 3 (1%) |
| **L74V** | 0 | 9 (18%) | 3 (2%) | 12 (5%) |
| **Y115F** | 0 | 2 (4%) | 0 | 2 (1%) |
| **M184V/I** | 34 (85%) | 22 (43%) | 70 (50%) | 126 (54%) |
| **TAMs[3]** | 3 (8%) | 2 (4%) | 4 (3%) | 9 (4%) |

1.Combivir is a fixed dose combination of lamivudine and zidovudine
2.Includes three non-virological failures and four unconfirmed virological failures.
3. Number of subjects with ≥1 Thymidine Analogue Mutations (TAMs).

TAMs might be selected when thymidine analogs are associated with abacavir. In a meta-analysis of six clinical trials, TAMs were not selected by regimens containing abacavir without zidovudine (0/127), but were selected by regimens containing abacavir and the thymidine analogue zidovudine (22/86, 26%).

*In vivo resistance (Therapy experienced patients)*

Clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. In a meta-analysis of five clinical trials where abacavir was added to intensify therapy, of 166 subjects, 123 (74%) had M184V/I, 50 (30%) had T215Y/F, 45 (27%) had M41L, 30 (18%) had K70R and 25 (15%) had D67N. K65R was absent and L74V and Y115F were uncommon (≤3%). Logistic regression modelling of the predictive value for genotype (adjusted for baseline plasma HIV-1 RNA [vRNA], CD4+ cell count, number and duration of prior antiretroviral therapies), showed that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at Week 4 ($p=0.015$) or 4 or more mutations at median Week 24 ($p\leq0.012$). In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, cause a high level of resistance to abacavir.

| Baseline Reverse Transcriptase Mutation | Week 4 (n = 166) | | |
|---|---|---|---|
| | n | Median Change vRNA ($log_{10}$ c/ml) | Percent with <400 copies/ml vRNA |
| **None** | 15 | -0.96 | 40% |
| **M184V alone** | 75 | -0.74 | 64% |
| **Any one NRTI mutation** | 82 | -0.72 | 65% |
| **Any two NRTI-associated mutations** | 22 | -0.82 | 32% |
| **Any three NRTI-associated mutations** | 19 | -0.30 | 5% |
| **Four or more NRTI-associated mutations** | 28 | -0.07 | 11% |

*Phenotypic resistance and cross-resistance*

Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple TAMs. Phenotypic cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir maintain their antiretroviral activities against such HIV-1 variants. The presence of M184V with K65R does give rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. The presence of M184V with Y115F gives rise to cross-resistance between abacavir and lamivudine. Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

Cross-resistance between abacavir and antiretrovirals from other classes (e.g. PIs or NNRTIs) is unlikely.

Clinical efficacy and safety

The demonstration of the benefit of Ziagen is mainly based on results of studies performed in adult treatment-naïve patients using a regimen of Ziagen 300 mg twice daily in combination with zidovudine and lamivudine.

*Twice daily (300 mg) administration:*

- *Therapy naïve adults*

In adults treated with abacavir in combination with lamivudine and zidovudine the proportion of patients with undetectable viral load (<400 copies/ml) was approximately 70% (intention to treat analysis at 48 weeks) with corresponding rise in CD4 cells.

One randomised, double blind, placebo controlled clinical study in adults has compared the combination of abacavir, lamivudine and zidovudine to the combination of indinavir, lamivudine and zidovudine. Due to the high proportion of premature discontinuation (42% of patients discontinued randomised treatment by week 48), no definitive conclusion can be drawn regarding the equivalence between the treatment regimens at week 48. Although a similar antiviral effect was observed between the abacavir and indinavir containing regimens in terms of proportion of patients with undetectable viral load (≤400 copies/ml; intention to treat analysis (ITT), 47% versus 49%; as treated analysis (AT), 86% versus 94% for abacavir and indinavir combinations respectively), results favoured the indinavir combination, particularly in the subset of patients with high viral load (>100,000 copies/ml at baseline; ITT, 46% versus 55%; AT, 84% versus 93% for abacavir and indinavir respectively).

In a multicentre, double-blind, controlled study (CNA30024), 654 HIV-infected, antiretroviral therapy-naïve patients were randomised to receive either abacavir 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg

once daily. The duration of double-blind treatment was at least 48 weeks. In the intent-to-treat (ITT) population, 70% of patients in the abacavir group, compared to 69% of patients in the zidovudine group, achieved a virologic response of plasma HIV-1 RNA ≤50 copies/ml by Week 48 (point estimate for treatment difference: 0.8, 95% CI -6.3, 7.9). In the as treated (AT) analysis the difference between both treatment arms was more noticeable (88% of patients in the abacavir group, compared to 95% of patients in the zidovudine group (point estimate for treatment difference: -6.8, 95% CI -11.8; -1.7). However, both analyses were compatible with a conclusion of non-inferiority between both treatment arms.

ACTG5095 was a randomised (1:1:1), double-blind, placebo-controlled trial performed in 1147 antiretroviral naïve HIV-1 infected adults, comparing 3 regimens: zidovudine (ZDV), lamivudine (3TC), abacavir (ABC), efavirenz (EFV) vs ZDV/3TC/EFV vs ZDV/3TC/ABC. After a median follow-up of 32 weeks, the tritherapy with the three nucleosides ZDV/3TC/ABC was shown to be virologically inferior to the two other arms regardless of baseline viral load (< or > 100 000 copies/ml) with 26% of subjects on the ZDV/3TC/ABC arm, 16% on the ZDV/3TC/EFV arm and 13% on the 4 drug arm categorised as having virological failure (HIV RNA >200 copies/ml). At week 48 the proportion of subjects with HIV RNA <50 copies/ml were 63%, 80% and 86% for the ZDV/3TC/ABC, ZDV/3TC/EFV and ZDV/3TC/ABC/EFV arms, respectively. The study Data Safety Monitoring Board stopped the ZDV/3TC/ABC arm at this time based on the higher proportion of patients with virologic failure. The remaining arms were continued in a blinded fashion. After a median follow-up of 144 weeks, 25% of subjects on the ZDV/3TC/ABC/EFV arm and 26% on the ZDV/3TC/EFV arm were categorised as having virological failure. There was no significant difference in the time to first virologic failure (p=0.73, log-rank test) between the 2 arms. In this study, addition of ABC to ZDV/3TC/EFV did not significantly improve efficacy.

| | | ZDV/3TC/ABC | ZDV/3TC/EFV | ZDV/3TC/ABC/EFV |
|---|---|---|---|---|
| Virologic failure (HIV RNA >200 copies/ml) | 32 weeks | 26% | 16% | 13% |
| | 144 weeks | - | 26% | 25% |
| Virologic success (48 weeks HIV RNA < 50 copies/ml) | | 63% | 80% | 86% |

- *Therapy experienced adults*

In adults moderately exposed to antiretroviral therapy the addition of abacavir to combination antiretroviral therapy provided modest benefits in reducing viral load (median change 0.44 $\log_{10}$ copies/ml at 16 weeks).

In heavily NRTI pretreated patients the efficacy of abacavir is very low. The degree of benefit as part of a new combination regimen will depend on the nature and duration of prior therapy which may have selected for HIV-1 variants with cross-resistance to abacavir.

*Once daily (600 mg) administration:*

- *Therapy naïve adults*

The once daily regimen of abacavir is supported by a 48 weeks multi-centre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. These were primarily asymptomatic HIV infected patients - Centre for Disease Control and Prevention (CDC) stage A. They were randomised to receive either abacavir 600 mg once daily or 300 mg twice daily, in combination with efavirenz and lamivudine given once daily. Similar clinical success (point estimate for treatment difference -1.7, 95% CI -8.4, 4.9) was observed for both regimens. From these results, it can be concluded with 95% confidence that the true difference is no greater than 8.4% in favour of the twice daily regimen. This potential difference is sufficiently small to draw an overall conclusion of non-inferiority of abacavir once daily over abacavir twice daily.

There was a low, similar overall incidence of virologic failure (viral load >50 copies/ml) in both the once and twice daily treatment groups (10% and 8% respectively). In the small sample size for genotypic analysis, 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. Long term data with abacavir used as a once daily regimen (beyond 48 weeks) are currently limited.

- *Therapy experienced adults*

In study CAL30001, 182 treatment-experienced patients with virologic failure were randomised and received treatment with either the fixed-dose combination of abacavir/lamivudine (FDC) once daily or abacavir 300 mg twice daily plus lamivudine 300 mg once daily, both in combination with tenofovir and a PI or an NNRTI for 48 weeks. Results indicate that the FDC group was non-inferior to the abacavir twice daily group, based on similar reductions in HIV-1 RNA as measured by average area under the curve minus baseline (AAUCMB, -1.65 $\log_{10}$ copies/ml versus -1.83 $\log_{10}$ copies/ml respectively, 95% CI -0.13, 0.38). Proportions with HIV-1 RNA < 50 copies/ml (50% versus 47%) and < 400 copies/ml (54% versus 57%) were also similar in each group (ITT population). However, as there were only moderately experienced patients included in this study with an imbalance in baseline viral load between the arms, these results should be interpreted with caution.

In study ESS30008, 260 patients with virologic suppression on a first line therapy regimen containing abacavir 300 mg plus lamivudine 150 mg, both given twice daily and a PI or NNRTI, were randomised to continue this regimen or switch to abacavir/lamivudine FDC plus a PI or NNRTI for 48 weeks. Results indicate that the FDC group was associated with a similar virologic outcome (non-inferior) compared to the abacavir plus lamivudine group, based on proportions of subjects with HIV-1 RNA < 50 copies/ml (90% and 85% respectively, 95% CI -2.7, 13.5).

*Additional information:*

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

Abacavir penetrates the cerebrospinal fluid (CSF) (see section 5.2), 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.

*Paediatric population:*

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/mlat 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 separate study comparing the unblinded NRTI combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA ≤400 copies/ml at 48 weeks, compared with those treated with lamivudine and zidovudine (47%)[ p=0.09, intention to treat analysis]. Similarly, greater proportions of children treated with the abacavir containing combinations had HIV-1 RNA ≤50 copies/ml at 48 weeks (53%, 42% and 28% respectively, p=0.07).

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.

## 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 therapeutic dosages a dosage of 300 mg twice daily, the mean (CV) steady state $C_{max}$ and $C_{min}$ of abacavir are approximately 3.00 μg/ml (30%) and 0.01 μg/ml(99%), respectively. The mean (CV) AUC over a dosing interval of 12 hours was 6.02 μg.h/ml (29%), equivalent to a 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 (CV) abacavir $C_{max}$ was approximately 4.26 μg/ml (28%) and the mean (CV) $AUC_{\infty}$ was 11.95 μg.h/ml (21%).

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 0.8 l/kg, indicating that abacavir penetrates freely into body tissues.

Studies in HIV infected patients have shown good penetration of abacavir into the CSF, with a CSF to plasma AUC ratio of between 30 to 44%. The observed values of the peak concentrations are 9 fold greater than the $IC_{50}$ of abacavir of 0.08 µg/ml or 0.26 µM when abacavir is given at 600 mg twice daily**.**

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 interactions with other medicinal products through plasma protein binding displacement.

Biotransformation

Abacavir is primarily metabolised by the liver with approximately 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. The metabolites are excreted in the urine.

Elimination

The mean half-life of abacavir is about 1.5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant accumulation of abacavir. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine. The remainder is eliminated in the faeces.

Intracellular pharmacokinetics

In a study of 20 HIV-infected patients receiving abacavir 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. In a crossover study in 27 HIV-infected patients, intracellular carbovir-TP exposures were higher for the abacavir 600 mg once daily regimen ($AUC_{24,ss}$ + 32 %, $C_{max24,ss}$ + 99 % and $C_{trough}$ + 18 %) compared to the 300 mg twice daily regimen. Overall, these data support the use of abacavir 600 mg once daily for the treatment of HIV infected patients. Additionally, the efficacy and safety of abacavir given once daily has been demonstrated in a pivotal clinical study (CNA30021- See section 5.1 Clinical experience).

Special patient populations

*Hepatic impairment*

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose; the median (range) AUC values was 24.1 (10.4 to 54.8) ug.h/ml. The results showed that there was a mean (90%CI) increase of 1.89 fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No definitive recommendation on dosage reduction is possible in patients with mild hepatic impairment due to the substantial variability of abacavir exposure.
Abacavir is not recommended in patients with moderate or severe hepatic impairment.

*Renal impairment*

Abacavir is primarily metabolised by the liver with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment. Based on limited experience Ziagen should be avoided in patients with end-stage renal disease.

*Paediatric population*
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 Stead-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% Cl) | Abacavir 8 mg/kg Twice-Daily Dosing Geometric Mean (95% Cl) | Once-Versus Twice-Daily Comparison GLS Mean Ratio (90% Cl) |
|---|---|---|---|---|
| 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.

*Elderly*

The pharmacokinetics of abacavir has not been studied in patients over 65 years of age.

## 5.3 Preclinical safety data

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

has a weak potential to cause chromosomal damage 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 rats in the thyroid gland of males and the liver, urinary bladder, lymph nodes and the subcutis of females.

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. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

In pre-clinical toxicology studies, abacavir treatment was shown to increase liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, autoinduction of abacavir metabolism or induction of the metabolism of other medicinal products hepatically metabolised has not been observed in man.

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.

In reproductive toxicity studies, embryo and foetal toxicity have been observed in rats but not in rabbits. These findings included decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and still births. No conclusion can be drawn with regard to the teratogenic potential of abacavir because of this embryo-foetal toxicity.

A fertility study in the rat has shown that abacavir had no effect on male or female fertility.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sorbitol 70% (E420)
Saccharin sodium
Sodium citrate
Citric acid anhydrous
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Propylene glycol (E1520)
Maltodextrin
Lactic acid
Glyceryl triacetate
Artificial strawberry and banana flavours
Purified water
Sodium hydroxide and/or hydrochloric acid for pH adjustment.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf-life

2 years

After first opening the container: 2 months

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Ziagen oral solution is supplied in high density polyethylene bottles with child-resistant closures, containing 240 ml of oral solution.

The pack also includes a polyethylene syringe-adapter and a 10 ml oral dosing syringe comprised of a polypropylene barrel (with ml graduations) and a polyethylene plunger.

### 6.6 Special precautions for disposal

A plastic adapter and oral dosing syringe are provided for accurate measurement of the prescribed dose of oral solution. The adapter is placed in the neck of the bottle and the syringe attached to this. The bottle is inverted and the correct volume withdrawn.
Any unused product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/112/002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 July 1999

Date of latest renewal: 21 March 2014

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFCTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

**Film-coated Tablets**

GlaxoSmithKline Pharmaceuticals S.A.
ul. Grunwaldzka 189
60-322 Poznan
Poland

**Oral Solution**

ViiV Healthcare Trading Services UK Limited
12 Riverwalk,
Citywest Business Campus
Dublin 24,
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I Summary of Product Characteristics, 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the date of the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON - TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Ziagen 300 mg film-coated tablets
Abacavir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg abacavir (as sulfate).

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated, scored tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

**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)

## 8. EXPIRY DATE

EXP {MM/YYYY}

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/112/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ziagen 300mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**TABLET BLISTER FOIL TEXT**

## 1. NAME OF THE MEDICINAL PRODUCT

Ziagen 300 mg tablets.

Abacavir

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

## 3. EXPIRY DATE

EXP {MM/YYYY}

## 4. BATCH NUMBER

Lot

## 5. OTHER

**ALERT CARD TEXT**

**SIDE 1**

**IMPORTANT - ALERT CARD**
**ZIAGEN (abacavir) tablets**
**Carry this card with you at all times**

Since Ziagen contains abacavir some 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 feeling ill

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

**( see reverse of card)**

**SIDE 2**

You should immediately contact your doctor if you think you are having a hypersensitivity reaction to Ziagen. Write your doctor's details below:

Doctor: .....…… Tel: .....……..

**If your doctor is not available, you must urgently seek alternative medical advice (e.g. the emergency unit of the nearest hospital).**

For general Ziagen information enquiries, contact GlaxoSmithKline….Tel …… (local company name and telephone number will be inserted here).

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON - ORAL SOLUTION**

## 1. NAME OF THE MEDICINAL PRODUCT

Ziagen 20 mg/ml oral solution
Abacavir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 20 mg of abacavir (as sulfate)

## 3. LIST OF EXCIPIENTS

Contains amongst others: sorbitol (340 mg/ml, E420), methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216). See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

240 ml oral solution

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

**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)

## 8. EXPIRY DATE

EXP {MM/YYYY}

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

Discard two months after first opening

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/112/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

ziagen 20mg/ml

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL - ORAL SOLUTION**

## 1. NAME OF THE MEDICINAL PRODUCT

Ziagen 20 mg/ml oral solution
Abacavir

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 20 mg of abacavir (as sulfate)

## 3. LIST OF EXCIPIENTS

Contains amongst others: sorbitol (340 mg/ml, E420), methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216). See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

240 ml oral solution

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP {MM/YYYY}

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

Discard two months after first opening

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/112/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

**ALERT CARD TEXT**

**SIDE 1**

**IMPORTANT - ALERT CARD**
**ZIAGEN (abacavir) oral solution**
**Carry this card with you at all times**

Since Ziagen contains abacavir some 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 feeling ill

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

**(see reverse of card)**

**SIDE 2**

You should immediately contact your doctor if you think you are having a hypersensitivity reaction to Ziagen. Write your doctor's details below:

Doctor: .....…… Tel: .....……..

**If your doctor is not available, you must urgently seek alternative medical advice (e.g. the emergency unit of the nearest hospital).**

For general Ziagen information enquiries, contact ……Tel …… (local company name and telephone number will be inserted here).

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Ziagen 300 mg Film-coated tablets**
Abacavir

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**IMPORTANT - Hypersensitivity reactions**

**Ziagen contains abacavir** (which is also an active substance in medicines such as **Kivexa, Triumeq** and **Trizivir**). Some people who take abacavir may develop a **hypersensitivity reaction** (a serious allergic reaction), which can be life-threatening if they continue to take abacavir containing products.

**You must carefully read all the information under 'Hypersensitivity reactions' in the panel in Section 4**.

The Ziagen pack includes an **Alert Card**, to remind you and medical staff about abacavir hypersensitivity. **Detach this card and keep it with you at all times**.

**What is in this leaflet**



## 1. What Ziagen is and what it is used for

**Ziagen is used to treat HIV (human immunodeficiency virus) infection.**

Ziagen contains the active ingredient abacavir. Abacavir belongs to a group of anti-retroviral medicines called *nucleoside analogue reverse transcriptase inhibitors (NRTIs)*.

Ziagen does not completely cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. It also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cell that are important in helping your body to fight infection.

Not everyone responds to treatment with Ziagen in the same way. Your doctor will monitor the effectiveness of your treatment.

## 2. What you need to know before you take Ziagen

**Do not take Ziagen:**

if you are **allergic** *(hypersensitive)* to abacavir (or any other medicine containing abacavir –such as **Trizivir**, **Triumeq** or **Kivexa**) or any of the other ingredients of this medicine (listed in Section 6)

**Carefully read all the information about hypersensitivity reactions in Section 4**.

**Check with your doctor** if you think this applies to you.

**Take special care with Ziagen**

Some people taking Ziagen for HIV are more at risk of serious side effects. You need to be aware of the extra risks:

- if you have **moderate or severe liver disease**
- if you have ever had **liver disease,** including hepatitis B or C
- if you are seriously **overweight** (especially if you are a woman)
- if you have **severe kidney disease**

**Talk to your doctor if any of these apply to you**. You may need extra check-ups, including blood tests, while you are taking your medicine. **See Section 4 for more information**.

Abacavir hypersensitivity reactions

Even patients who don't have the HLA-B*5701 gene may still develop a **hypersensitivity reaction** (a serious allergic reaction).

**Carefully read all the information about hypersensitivity reactions in Section 4 of this leaflet.**

Risk of heart attack

It cannot be excluded that abacavir may increase the risk of having a heart attack.

**Tell your doctor** if you have heart problems, if you smoke, or have other illnesses that may increase your risk of heart disease such as high blood pressure, or diabetes. Do not stop taking Ziagen unless your doctor advises you to do so.

Look out for important symptoms

Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking Ziagen.

**Read the information 'Other possible side effects of combination therapy for HIV' in Section 4 of this leaflet**.

Protect other people

HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

**Other medicines and Ziagen**

**Tell your doctor or pharmacist if you are taking any other medicines**, or if you have taken any recently, including herbal medicines or other medicines you bought without a prescription. Remember to tell your doctor or pharmacist if you begin taking a new medicine while you are taking Ziagen.

**Some medicines interact with Ziagen**

These include:

- **phenytoin**, for treating **epilepsy**

  **Tell your doctor** if you are taking phenytoin. Your doctor may need to monitor you while you are taking Ziagen.

- **methadone** used as a **heroin substitute**. Abacavir increases the rate at which methadone is removed from the body. If you are taking methadone, you will be checked for any withdrawal symptoms. Your methadone dose may need to be changed.
  **Tell your doctor** if you are taking methadone.

- **Riociguat,** for treating **high blood pressure in the blood vessels** (the pulmonary arteries) that carry blood from the heart to the lungs. Your doctor may need to reduce your riociguat dose, as abacavir may increase riociguat blood levels.

**Pregnancy**
**Ziagen is not recommended for use during pregnancy**. Ziagen and similar medicines may cause side effects in unborn babies. If you have taken Ziagen during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

**Breast-feeding**
**Women who are HIV-positive must not breast-feed**, because HIV infection can be passed on to the baby in breast milk. A small amount of the ingredients in Ziagen can also pass into your breast milk. If you are breast-feeding, or thinking about breast-feeding:
**Talk to your doctor immediately**.

**Driving and using machines**
**Do not drive or operate machines** unless you are feeling well.

**Important information about some of the other ingredients of Ziagen tablets.**
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

## 3. How to take Ziagen

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Swallow the tablets with some water. Ziagen can be taken with or without food.

If you cannot swallow the tablet(s), you may crush and combine them with a small amount of food or drink, and take all the dose immediately.

**Stay in regular contact with your doctor**
Ziagen helps to control your condition. You need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.
**Keep in touch with your doctor, and do not stop taking Ziagen** without your doctor's advice.

**How much to take**

**Adults, adolescents and children weighing at least 25 kg**

**The usual dose of Ziagen is 600 mg a day**. This can be taken either as one 300 mg tablet twice a day or two 300 mg tablets once a day.

**Children from one year of age weighing less than 25 kg**

The dose given depends on the body weight of your child. The recommended dose is:

- **Children weighing at least 20 kg and less than 25 kg:** The usual dose of Ziagen is 450 mg a day. This can be given as 150 mg (half of a tablet) taken in the morning and 300 mg (one whole tablet) taken in the evening, or 450 mg (one and a half tablets) once a day as advised by your doctor.
- **Children weighing at least 14 kg and less than 20 kg:** The usual dose of Ziagen is 300 mg a day. This can be given as 150 mg (half of a tablet) twice daily, or 300 mg (one whole tablet) once a day as advised by your doctor.

The tablet can be divided into equal doses.

An oral solution (20 mg abacavir/ml) is also available for the treatment of children over three months of age and weighing less than 14 kg, or for people who need a lower than usual dose, or who cannot take tablets.

**If you take more Ziagen than you should**
If you accidentally take too much Ziagen, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

**If you forget to take Ziagen**
If you forget to take a dose, take it as soon as you remember. Then continue your treatment as before. Do not take a double dose to make up for a forgotten dose.

It is important to take Ziagen regularly, because if you take it at irregular intervals, you may be more likely to have a hypersensitivity reaction.

**If you have stopped taking Ziagen**
If you have stopped taking Ziagen for any reason - especially because you think you are having side effects, or because you have other illness:

**Talk to your doctor before you start taking it again**. Your doctor will check whether your symptoms were related to a hypersensitivity reaction. If the doctor thinks they may have been related, **you will be told never again to take Ziagen, or any other medicine containing abacavir (e.g. Triumeq,Trizivir or Kivexa)**. It is important that you follow this advice.

If your doctor advises that you can start taking Ziagen again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it.

## 4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everyone gets them.

When you are being treated for HIV, it can be hard to tell whether a symptom is a side effect of Ziagen or other medicines you are taking, or an effect of the HIV disease itself. **So it is very important to talk to your doctor about any changes in your health**.

Even patients who don't have the HLA-B*5701 gene may still develop **a hypersensitivity reaction** (a serious allergic reaction), described in this leaflet in the panel headed 'Hypersensitivity reactions'.

**It is very important that you read and understand the information about this serious reaction**.

**As well as the side effects listed below for Ziagen**, other conditions can develop during combination therapy for HIV.
It is important to read the information later in this section under 'Other possible side effects of combination therapy for HIV'.

**Hypersensitivity reactions**

**Ziagen** contains **abacavir** (which is also an active substance in **Trizivir** , **Triumeq** and **Kivexa**). Abacavir can cause a serious allergic reaction known as a hypersensitivity reaction.
These hypersensitivity reactions have been seen more frequently in people taking medicines that contain abacavir.

**Who gets these reactions?**
Anyone taking Ziagen could develop a hypersensitivity reaction to abacavir, which could be life threatening if they continue to take Ziagen.

You are more likely to develop such a reaction if you have the **HLA-B*5701** gene (but you can get a reaction even if you do not have this gene). You should have been tested for this gene before Ziagen was prescribed for you. **If you know you have this gene, tell your doctor before you take Ziagen**.
About 3 to 4 in every 100 patients treated with abacavir in a clinical trial who did not have the HLA-B*5701 gene developed a hypersensitivity reaction.

**What are the symptoms?**
The most common symptoms are:
- **fever** (high temperature) and **skin rash**

Other common symptoms are:
- nausea (feeling sick), vomiting (being sick), diarrhoea, abdominal (stomach) pain, severe tiredness

Other symptoms include:

Pains in the joints or muscles, swelling of the neck, shortness of breath, sore throat, cough, occasional headaches, inflammation of the eye (conjunctivitis), mouth ulcers, low blood pressure, tingling or numbness of the hands or feet.

**When do these reactions happen?**
Hypersensitivity reactions can start at any time during treatment with Ziagen, but are more likely during the first 6 weeks of treatment.

**If you are caring for a child who is being treated with Ziagen, it is important that you understand the information about this hypersensitivity reaction. If your child gets the symptoms described below it is essential that you follow the instructions given.**

**Contact your doctor immediately:**
**1 if you get a skin rash, OR**
**2 if you get symptoms from at least 2 of the following groups:**
- fever
- shortness of breath, sore throat or cough
- nausea or vomiting, diarrhoea or abdominal pain
- severe tiredness or achiness, or generally feeling ill

**Your doctor may advise you to stop taking Ziagen**.

**If you have stopped taking Ziagen**

If you have stopped taking Ziagen because of a hypersensitivity reaction, **you must NEVER AGAIN take Ziagen, or any other medicine containing abacavir (e.g. Trizivir, Triumeq or Kivexa)**. If you do, within hours, your blood pressure could fall dangerously low, which could result in death.

If you have stopped taking Ziagen for any reason - especially because you think you are having side effects, or because you have other illness:

**Talk to your doctor before you start again**. Your doctor will check whether your symptoms were related to a hypersensitivity reaction. If the doctor thinks they may have been, **you will then be told never again to take Ziagen, or any other medicine containing abacavir (e.g. Trizivir, Triumeq or Kivexa)**. It is important that you follow this advice.

Occasionally, hypersensitivity reactions have developed in people who start taking abacavir containing products again, but who had only one symptom on the Alert Card before they stopped taking it.

Very rarely, patients who have taken medicines containing abacavir in the past without any symptoms of hypersensitivity have developed a hypersensitivity reaction when they start taking these medicines again.

If your doctor advises that you can start taking Ziagen again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it.

**If you are hypersensitive to Ziagen, return all your unused Ziagen tablets for safe disposal.** Ask your doctor or pharmacist for advice.

The Ziagen pack includes an **Alert Card**, to remind you and medical staff about hypersensitivity reactions. **Detach this card and keep it with you at all times**.

**Common side effects**
These may affect **up to 1 in 10** people:
- hypersensitivity reaction
- feeling sick *(nausea)*
- headache
- being sick *(vomiting)*
- diarrhoea
- loss of appetite
- tiredness, lack of energy
- fever (high temperature)
- skin rash

**Rare side effects**
These may affect **up to 1 in 1,000** people:
- inflammation of the pancreas *(pancreatitis)*

**Very rare side effects**
These may affect **up to 1 in 10,000** people:
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme)*
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals *(Stevens–Johnson syndrome)*, and a more severe form causing skin peeling in more than 30% of the body surface *(toxic epidermal necrolysis)*
- lactic acidosis (excess lactic acid in the blood)

**If you notice any of these symptoms contact a doctor urgently**.

**If you get side effects**

**Tell your doctor or pharmacist** if any of the side effects get severe or troublesome, or if you notice any side effects not listed in this leaflet.

**Other possible side effects of combination therapy for HIV**

Combination therapy including Ziagen may cause other conditions to develop during HIV treatment.

**Symptoms of infection and inflammation**

**Old infections may flare up**
People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (*opportunistic infections*). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections. Symptoms usually include **fever**, plus some of the following:
- headache
- stomach ache
- difficulty breathing

In rare cases, as the immune system becomes stronger, it can also attack healthy body tissue (*autoimmune disorders*). The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection. Symptoms may include:
- palpitations (rapid or irregular heartbeat) or tremor
- hyperactivity (excessive restlessness and movement)
- weakness beginning in the hands and feet and moving up towards the trunk of the body

If you get any symptoms of infection while you are taking Ziagen:
**Tell your doctor immediately**. Do not take other medicines for the infection without your doctor's advice.

**You may have problems with your bones**

Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:
- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids

- if they drink alcohol
- if their immune systems are very weak
- if they are overweight

**Signs of osteonecrosis include:**
- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving

If you notice any of these symptoms:
**Tell your doctor**.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Ziagen

Keep this medicine out of the sight and reach of children.

Do not take this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures help protect the environment.

## 6. Contents of the pack and other information

**What Ziagen contains**
The active substance in each Ziagen film-coated, scored tablet is 300 mg of abacavir (as sulfate).

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

**What Ziagen looks like and contents of the pack**
Ziagen film-coated tablets are engraved with ‘GX 623’ on both sides. The scored tablets are yellow and capsule-shaped and are provided in blister packs containing 60 tablets.

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**Manufacturer:**
GlaxoSmithKline Pharmaceuticals S.A., ul., Grunwaldzka 189, 60-322 Poznan, Poland.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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**This leaflet was last revised in {MM/YYYY}**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

**Package leaflet: Information for the user**

**Ziagen 20 mg/ml oral solution**
Abacavir

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**IMPORTANT - Hypersensitivity reactions**

**Ziagen contains abacavir** (which is also an active substance in medicines such as **Kivexa**,**Triumeq** and **Trizivir**). Some people who take abacavir may develop a **hypersensitivity reaction** (a serious allergic reaction), which can be life-threatening if they continue to take abacavir. containing products.

**You must carefully read all the information under 'Hypersensitivity reactions' in the panel in Section 4**.

The Ziagen pack includes an **Alert Card**, to remind you and medical staff about abacavir hypersensitivity. **Detach this card and keep it with you at all times**.

**What is in this leaflet**



## 1. What Ziagen is and what it is used for

**Ziagen is used to treat HIV (human immunodeficiency virus) infection**.

Ziagen contains the active ingredient abacavir. Abacavir belongs to a group of anti-retroviral medicines called *nucleoside analogue reverse transcriptase inhibitors (NRTIs)*.

Ziagen does not completely cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. It also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cell that are important in helping your body to fight infection.

Not everyone responds to treatment with Ziagen in the same way. Your doctor will monitor the effectiveness of your treatment.

## 2. What you need to know before you take Ziagen

**Do not take Ziagen:**

- if you are **allergic** (*hypersensitive*) to abacavir (or any other medicine containing abacavir - such as **Triumeq, Trizivir** or **Kivexa**) or any of the other ingredients of this medicine (listed in Section 6)
  **Carefully read all the information about hypersensitivity reactions in Section 4**.
  **Check with your doctor** if you think this applies to you.

**Take special care with Ziagen**

Some people taking Ziagen for HIV are more at risk of serious side effects. You need to be aware of the extra risks:

- if you have moderate or **severe liver disease**
- if you have ever had **liver disease,** including hepatitis B or C
- if you are seriously **overweight** (especially if you are a woman)
- if you have **severe kidney disease**
  **Talk to your doctor if any of these apply to you**. You may need extra check-ups, including blood tests, while you are taking your medicine. **See Section 4 for more information**.

Abacavir hypersensitivity reactions

Even patients who don't have the HLA-B*5701 gene may still develop a **hypersensitivity reaction** (a serious allergic reaction).

**Carefully read all the information about hypersensitivity reactions in Section 4 of this leaflet.**

**Risk of heart attack**

It cannot be excluded that abacavir may increase the risk of having a heart attack.
**Tell your doctor** if you have heart problems, if you smoke, or have other illnesses that may increase your risk of heart disease such as high blood pressure, or diabetes. Do not stop taking Ziagen unless your doctor advises you to do so.

**Look out for important symptoms**

Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking Ziagen.
**Read the information 'Other possible side effects of combination therapy for HIV' in Section 4 of this leaflet**.

**Protect other people**

HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

**Other medicines and Ziagen**

**Tell your doctor or pharmacist if you are taking any other medicines**, or if you have taken any recently, including herbal medicines or other medicines you bought without a prescription. Remember to tell your doctor or pharmacist if you begin taking a new medicine while you are taking Ziagen.

**Some medicines interact with Ziagen**

These include:

- **phenytoin**, for treating **epilepsy**.
  **Tell your doctor** if you are taking phenytoin. Your doctor may need to monitor you while you are taking Ziagen.

- **methadone** used as a **heroin substitute.** Abacavir increases the rate at which methadone is removed from the body. If you are taking methadone, you will be checked for any withdrawal symptoms. Your methadone dose may need to be changed.

**Tell your doctor** if you are taking methadone.

- **Riociguat,** for treating **high blood pressure in the blood vessels** (the pulmonary arteries) that carry blood from the heart to the lungs. Your doctor may need to reduce your riociguat dose, as abacavir may increase riociguat blood levels.

**Pregnancy**
**Ziagen is not recommended for use during pregnancy**. Ziagen and similar medicines may cause side effects in unborn babies. If you have taken Ziagen during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

**Breast-feeding**
**Women who are HIV-positive must not breast-feed**, because HIV infection can be passed on to the baby in breast milk. A small amount of the ingredients in Ziagen can also pass into your breast milk.

If you are breast-feeding, or thinking about breast-feeding:
**Talk to your doctor immediately**.

**Driving and using machines**
**Do not drive or operate machines** unless you are feeling well.

**Important information about some of the other ingredients of Ziagen oral solution**

This medicine contains the sweetener sorbitol (approximately 5g in each 15 ml dose), which may have a mild laxative effect. Do not take medicines containing sorbitol if you have hereditary fructose intolerance. The calorific value of sorbitol is 2.6 kcal/g.

Ziagen also contains preservatives *(parahydroxybenzoates)* which may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

## 3. How to take Ziagen

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Ziagen can be taken with or without food.

**Stay in regular contact with your doctor**
Ziagen helps to control your condition. You need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.
**Keep in touch with your doctor, and do not stop taking Ziagen** without your doctor’s advice.

**How much to take**

**Adults, adolescents and children weighing at least 25 kg**

**The usual dose of Ziagen is 600 mg (30 ml) a day.** This can be taken either as 300 mg (15 ml) twice a day or 600 mg (30 ml) once a day.

**Children from 3 months of age weighing less than 25 kg**

The dose depends on the child's body weight. The recommended dose is 8 mg/kg twice a day or 16 mg/kg once a day, up to a maximum total daily dose of 600 mg daily.

**How to measure the dose and take the medicine**

Use the oral dosing syringe supplied with the pack to measure your dose accurately. When full, the syringe contains 10 ml of solution.

1. Remove the plastic wrap from the syringe/adapter
2.. **Remove the bottle cap.** Keep it safely.
3. Remove the adapter from the syringe.
4.. Hold the bottle firmly. **Push the plastic adapter into the neck of the bottle**
5. **Insert the syringe** firmly into the adapter
6. Turn bottle upside down
7. **Pull out the syringe plunger** until the syringe contains the first part of your full dose
8. Turn the bottle the right way up. **Remove the syringe** from the adapter
9. **Put the syringe into your mouth,** placing the tip of the syringe against the inside of your cheek. **Slowly push the plunger in,** allowing time to swallow. **Don't** push too hard and squirt the liquid into the back of your throat, or you may choke
10. **Repeat steps 5 to 9** in the same way until you have taken your whole dose. *For example, if your dose is 30 ml, you need to take 3 syringe-fulls of medicine*
11. **Take the syringe out of the bottle** and **wash** it thoroughly in clean water. Let it dry completely before you use it again
12. **Close the bottle** tightly with the cap, leaving the adapter in place

**If you take more Ziagen than you should**
If you accidentally take too much Ziagen, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

**If you forget to take Ziagen**
If you forget to take a dose, take it as soon as you remember. Then continue your treatment as before. Do not take a double dose to make up for a forgotten dose.

It is important to take Ziagen regularly, because if you take it at irregular intervals, you may be more likely to have a hypersensitivity reaction.

**If you have stopped taking Ziagen**
If you have stopped taking Ziagen for any reason - especially because you think you are having side effects, or because you have other illness:

**Talk to your doctor before you start taking it again**. Your doctor will check whether your symptoms were related to a hypersensitivity reaction. If the doctor thinks they may have been related, **you will be told never again to take Ziagen, or any other medicine containing abacavir (e.g.Triumeq, Trizivir or Kivexa)**. It is important that you follow this advice.

If your doctor advises that you can start taking Ziagen again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it.

## 4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everyone gets them.

When you are being treated for HIV, it can be hard to tell whether a symptom is a side effect of Ziagen or other medicines you are taking, or an effect of the HIV disease itself. **So it is very important to talk to your doctor about any changes in your health**.

Even patients who don't have the HLA-B*5701 gene may still develop **a hypersensitivity reaction** (a serious allergic reaction), described in this leaflet in the panel headed 'Hypersensitivity reactions'.

**It is very important that you read and understand the information about this serious reaction**.

**As well as the side effects listed below for Ziagen**, other conditions can develop during combination therapy for HIV.

It is important to read the information later in this section under 'Other possible side effects of combination therapy for HIV'.

**Hypersensitivity reactions**

**Ziagen** contains **abacavir** (which is also an active substance in **Kivexa, Triumeq** and **Trizivir**). Abacavir can cause a serious allergic reaction known as a hypersensitivity reaction.
These hypersensitivity reactions have been seen more frequently in people taking medicines that contain abacavir.

**Who gets these reactions?**
Anyone taking Ziagen could develop a hypersensitivity reaction to abacavir, which could be life threatening if they continue to take Ziagen.

You are more likely to develop such a reaction if you have the **HLA-B*5701** gene (but you can get a reaction even if you do not have this gene). You should have been tested for this gene before Ziagen was prescribed for you. **If you know you have this gene, tell your doctor before you take Ziagen.**

About 3 to 4 in every 100 patients treated with abacavir in a clinical trial who did not have the HLA-B*5701 gene developed a hypersensitivity reaction.

**What are the symptoms?**

The most common symptoms are:
- **fever** (high temperature) and **skin rash**

Other common symptoms are:
- nausea (feeling sick), vomiting (being sick), diarrhoea, abdominal (stomach) pain, severe tiredness

Other symptoms include:
Pains in the joints or muscles, swelling of the neck, shortness of breath, sore throat, cough, occasional headaches, inflammation of the eye (conjunctivitis), mouth ulcers, low blood pressure, tingling or numbness of the hands or feet.

**When do these reactions happen?**

Hypersensitivity reactions can start at any time during treatment with Ziagen, but are more likely during the first 6 weeks of treatment.

**If you are caring for a child who is being treated with Ziagen, it is important that you understand the information about this hypersensitivity reaction. If your child gets the symptoms described below it is essential that you follow the instructions given.**

**Contact your doctor immediately:**
**1 if you get a skin rash, OR**
**2 if you get symptoms from at least 2 of the following groups:**
- fever
- shortness of breath, sore throat or cough
- nausea or vomiting, diarrhoea or abdominal pain
- severe tiredness or achiness, or generally feeling ill

**Your doctor may advise you to stop taking Ziagen**.

**If you have stopped taking Ziagen**

If you have stopped taking Ziagen because of a hypersensitivity reaction, **you must NEVER AGAIN take Ziagen, or any other medicine containing abacavir (e.g. Trizivir, Triumeq or Kivexa)**. If you do, within hours, your blood pressure could fall dangerously low, which could result in death.

If you have stopped taking Ziagen for any reason - especially because you think you are having side effects, or because you have other illness:

**Talk to your doctor before you start again**. Your doctor will check whether your symptoms were related to a hypersensitivity reaction. If the doctor thinks they may have been, **you will then be told never again to take Ziagen, or any other medicine containing abacavir (e.g. Trizivir , Triumeq or Kivexa)**. It is important that you follow this advice.

Occasionally, hypersensitivity reactions have developed in people who start taking abacavir containing products again, but who had only one symptom on the Alert Card before they stopped taking it.

Very rarely, patients who have taken medicines containing abacavir in the past without any symptoms of hypersensitivity have developed a hypersensitivity reaction when they start taking these medicines again.

If your doctor advises that you can start taking Ziagen again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it.

**If you are hypersensitive to Ziagen, return all your unused Ziagen oral solution for safe disposal.** Ask your doctor or pharmacist for advice.

The Ziagen pack includes an **Alert Card**, to remind you and medical staff about hypersensitivity reactions. **Detach this card and keep it with you at all times**.

**Common side effects**
These may affect **up to 1 in 10** people:
- hypersensitivity reaction
- feeling sick *(nausea)*
- headache
- being sick *(vomiting)*
- diarrhoea
- loss of appetite
- tiredness, lack of energy
- fever (high temperature)
- skin rash

**Rare side effects**
These may affect **up to 1 in 1,000** people:
- inflammation of the pancreas *(pancreatitis)*

**Very rare side effects**
These may affect **up to 1 in 10,000** people:
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme)*
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals *(Stevens–Johnson syndrome)*, and a more severe form causing skin peeling in more than 30% of the body surface *(toxic epidermal necrolysis)*.
- lactic acidosis (excess lactic acid in the blood)

**If you notice any of these symptoms contact a doctor urgently**.

**If you get side effects**

**Tell your doctor or pharmacist** if any of the side effects gets severe or troublesome, or if you notice any side effects not listed in this leaflet.

**Other possible side effects of combination therapy for HIV**

Combination therapy including Ziagen may cause other conditions to develop during HIV treatment.

**Symptoms of infection and inflammation**

**Old infections may flare up**

People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections. Symptoms usually include **fever**, plus some of the following:
- headache
- stomach ache
- difficulty breathing

In rare cases, as the immune system becomes stronger, it can also attack healthy body tissue (*autoimmune disorders*). The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection. Symptoms may include:
- palpitations (rapid or irregular heartbeat) or tremor
- hyperactivity (excessive restlessness and movement)
- weakness beginning in the hands and feet and moving up towards the trunk of the body

If you get any symptoms of infection while you are taking Ziagen:
**Tell your doctor immediately**. Do not take other medicines for the infection without your doctor's advice.

**You may have problems with your bones**

Some people taking combination therapy for HIV develop a condition called *osteonecrosis*. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:
- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol

- if their immune systems are very weak
- if they are overweight

**Signs of osteonecrosis include:**
- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving

If you notice any of these symptoms:
**Tell your doctor**.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Ziagen

Keep this medicine out of the sight and reach of children.

Do not take this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Do not store above 30°C.

Discard oral solution two months after first opening.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures protect the environment.

## 6. Contents of the pack and other information

**What Ziagen contains**
The active substance in Ziagen oral solution is 20 mg of abacavir (as sulfate) in each ml of the solution.

The other ingredients are sorbitol 70% (E420), saccharin sodium, sodium citrate, citric acid anhydrous, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), propylene glycol (E1520), maltodextrin, lactic acid, glyceryl triacetate, artificial strawberry and banana flavour, purified water, sodium hydroxide and/or hydrochloric acid for pH adjustment.

**What Ziagen looks like and contents of the pack**
Ziagen oral solution is clear to yellowish in colour which may turn into a brown colour over time with strawberry/banana flavouring. It is supplied in cartons containing a white polyethylene bottle, with a child resistant cap. The bottle contains 240 ml (20 mg abacavir/ml) of solution. A 10 ml oral dosing syringe and a plastic adapter for the bottle are included in the pack.

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**Manufacturer:** ViiV Healthcare Trading Services UK Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland

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