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 a 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.

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. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see “Management after an interruption of Ziagen therapy”). Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing (see section 4.4 and 4.8).

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 and adolescents (over 12 years of age):** 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).

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

**Children (under 12 years of age):**

A dosing according to weight bands is recommended for Ziagen tablets. This dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling. A pharmacokinetic overexposure of abacavir can occur since accurate dosing cannot be achieved with this formulation. Therefore a close safety monitoring is warranted in these patients.

Children weighing at least 30 kg: the adult dosage of 300 mg twice daily should be taken.

Children weighing ≥ 21 kg to < 30 kg: one half of a Ziagen tablet taken in the morning and one whole tablet taken in the evening.

Children weighing 14 to 21 kg: one half of a Ziagen tablet twice daily.

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

**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 dose recommendation can be made in patients with mild hepatic impairment. In patients with moderate hepatic impairment, no data are available, therefore the use of abacavir is not recommended unless judged necessary. If abacavir is used in patients with mild or moderate hepatic impairment, then close monitoring is required, and if feasible, monitoring of abacavir plasma levels is recommended (see section 5.2). Abacavir is contraindicated in patients with severe hepatic impairment (see section 4.3 and 4.4).

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

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. See BOXED INFORMATION ON HYPERSENSITIVITY REACTIONS in sections 4.4. and 4.8.

Severe hepatic impairment.

### 4.4 Special warnings and precautions for use

**Hypersensitivity reaction** (see also section 4.8):

In a clinical study, 3.4% of subjects with a negative HLA-B*5701 status receiving abacavir developed a hypersensitivity reaction.

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. Based on the prospective study CNA106030 (PREDICT-1), use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele significantly reduced the incidence of abacavir hypersensitivity.
reactions. In populations similar to that enrolled in the PREDICT-1 study, it is estimated that 48% to 61% of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0% to 4% of patients who do not have the HLA-B*5701 allele.

These results are consistent with those of prior retrospective studies.

As a consequence, 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. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see “Management after an interruption of Ziagen therapy”). Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available based on the treatment history and resistance testing (see section 4.1).

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. It is noteworthy that among patients with a clinically suspected hypersensitivity reaction, a proportion did not carry HLA-B*5701. Therefore, even in the absence of HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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

- **Clinical description**

Hypersensitivity reactions are characterised by the appearance of symptoms indicating multi-organ system involvement. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome.

Other signs and symptoms may include respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised), gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia).

The symptoms related to this hypersensitivity reaction worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of Ziagen.

- **Clinical management**

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

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

Ziagen, or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir), MUST NEVER be restarted in patients who have stopped therapy due to a hypersensitivity reaction. Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.
To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, Ziagen must be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications).

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

- **Management after an interruption of Ziagen therapy**

Regardless of a patient’s HLA-B*5701 status, if therapy with Ziagen has been discontinued for any reason and restarting therapy is under consideration, the reason for discontinuation must be established to assess whether the patient had any symptoms of a hypersensitivity reaction. **If a hypersensitivity reaction cannot be ruled out, Ziagen or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir) must not be restarted.**

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting Ziagen in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping Ziagen. The most common isolated symptom of a hypersensitivity reaction was a skin rash. Moreover, on very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction (i.e. patients previously considered to be abacavir tolerant). In both cases, if a decision is made to restart Ziagen this must be done in a setting where medical assistance is readily available.

Screening for carriage of the HLA-B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir in such patients who test positive for the HLA-B*5701 allele is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and with close medical supervision.

- **Essential patient information**

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

- patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.

- patients must also be informed that a HLA-B*5701 negative patient can also experience an abacavir hypersensitivity reaction. Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir **MUST CONTACT THEIR DOCTOR IMMEDIATELY.**

- patients who are hypersensitive to abacavir should be reminded that they must never take Ziagen or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir) again, regardless of their HLA-B*5701 status.

- in order to avoid restarting Ziagen, patients who have experienced a hypersensitivity reaction should be asked to return the remaining Ziagen tablets or oral solution to the pharmacy.

- patients who have stopped Ziagen for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.
- each patient should be reminded to read the Package Leaflet included in the Ziagen pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

**Lactic acidosis:** lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

**Mitochondrial dysfunction:** nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

**Lipodystrophy:** combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

**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 contraindicated in patients with severe hepatic impairment (see section 4.3). 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.

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.

A pharmacokinetic study has been performed in patients with mild hepatic impairment. However, a definitive recommendation on dose reduction is not possible due to substantial variability of drug exposure in this patient population (see section 5.2). The clinical safety data available with abacavir in heptatically impaired patients is very limited. Due to the potential increases in exposure (AUC) in some patients, close monitoring is required. No data are available in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to substantially increase in these patients. Therefore, the use of abacavir in patients with moderate hepatic impairment is not recommended unless judged necessary and requires close monitoring of these patients.

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

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.

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

Opportunistic infections: patients receiving Ziagen or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission: patients should be advised that current antiretroviral therapy, including Ziagen, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Myocardial Infarction: 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 try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

4.5 Interaction with other medicinal products and other forms of interaction

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for P450 mediated interactions with other medicinal products involving abacavir is low. P450 does not play a major role in the metabolism of abacavir, and abacavir does not inhibit metabolism mediated by CYP 3A4. Abacavir has also been shown *in vitro* not to inhibit CYP 3A4, 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\textsubscript{max} and a one hour delay in t\textsubscript{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.

4.6 Pregnancy and lactation

Ziagen is not recommended during pregnancy. The safe use of abacavir in human pregnancy has not been established. Placental transfer of abacavir and/or its related metabolites has been shown to occur in animals. Toxicity to the developing embryo and foetus occurred in rats, but not in rabbits (see section 5.3). The teratogenic potential of abacavir could not be established from studies in animals.

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

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

**Hypersensitivity** (see also section 4.4):

In a clinical study, 3.4 % of subjects with a negative HLA-B*5701 status receiving abacavir...
developed a hypersensitivity reaction. In clinical studies with abacavir 600 mg once daily the reported rate of hypersensitivity remained within the range recorded for abacavir 300 mg twice daily.

Some hypersensitivity reactions were life-threatening and resulted in fatal outcome despite taking precautions. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

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

The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in at least 10% of patients with a hypersensitivity reaction are in bold text.

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

Rash (81% vs 67% respectively) and gastrointestinal manifestations (70% vs 54% respectively) were more frequently reported in children compared to adults.

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. This delay in diagnosis of hypersensitivity has resulted in Ziagen being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases.

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. Close medical supervision is necessary during the first two months, with consultations every two weeks.

It is likely that intermittent therapy may increase the risk of developing sensitisation and therefore occurrence of clinically significant hypersensitivity reactions. Consequently, patients should be advised of the importance of taking Ziagen regularly.

Restarting Ziagen following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction is usually more severe than on initial presentation, and may include life-threatening hypotension and death. Regardless of their HLA-
B*5701 status, patients who develop this hypersensitivity reaction must discontinue Ziagen and must never be rechallenged with Ziagen, or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir).

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, Ziagen must be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications).

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting Ziagen in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping Ziagen. The most common isolated symptom of a hypersensitivity reaction was a skin rash. Moreover, on very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity reaction. In both cases, if a decision is made to restart Ziagen this must be done in a setting where medical assistance is readily available.

Each patient must be warned about this hypersensitivity reaction to abacavir.

For many of the other 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 those 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 reaction. If Ziagen has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart a medicinal product containing abacavir, this must be done in a setting where medical assistance is readily available (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

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

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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 (see section 4.4).

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

**Laboratory abnormalities**

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.

### 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. Abacavir shows synergy *in vitro* in combination with nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, lamivudine and stavudine.

*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 EC₅₀ 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%).
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Abacavir + Combivir$^1$</th>
<th>Abacavir + lamivudine + NNRTI</th>
<th>Abacavir + lamivudine + PI (or PI/ritonavir)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>282</td>
<td>1094</td>
<td>909</td>
<td>2285</td>
</tr>
<tr>
<td><strong>Number of Virological Failures</strong></td>
<td>43</td>
<td>90</td>
<td>158</td>
<td>306</td>
</tr>
<tr>
<td><strong>Number of On-Therapy Genotypes</strong></td>
<td>40 (100%)</td>
<td>51 (100%)$^2$</td>
<td>141 (100%)</td>
<td>232 (100%)</td>
</tr>
<tr>
<td>K65R</td>
<td>0</td>
<td>1 (2%)</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>L74V</td>
<td>0</td>
<td>9 (18%)</td>
<td>3 (2%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Y115F</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>M184V/I</td>
<td>34 (85%)</td>
<td>22 (43%)</td>
<td>70 (50%)</td>
<td>126 (54%)</td>
</tr>
<tr>
<td>TAMs$^3$</td>
<td>3 (8%)</td>
<td>2 (4%)</td>
<td>4 (3%)</td>
<td>9 (4%)</td>
</tr>
</tbody>
</table>

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 $\geq$ 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 ($\leq$ 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$$\leq$0.012). 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.
<table>
<thead>
<tr>
<th>Baseline Reverse Transcriptase Mutation</th>
<th>Week 4 (n = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>None</td>
<td>15</td>
</tr>
<tr>
<td>M184V alone</td>
<td>75</td>
</tr>
<tr>
<td>Any one NRTI mutation</td>
<td>82</td>
</tr>
<tr>
<td>Any two NRTI-associated mutations</td>
<td>22</td>
</tr>
<tr>
<td>Any three NRTI-associated mutations</td>
<td>19</td>
</tr>
<tr>
<td>Four or more NRTI-associated mutations</td>
<td>28</td>
</tr>
</tbody>
</table>

**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 Experience**

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.

<table>
<thead>
<tr>
<th>Virologic failure (HIV RNA &gt;200 copies/ml)</th>
<th>ZDV/3TC/ABC</th>
<th>ZDV/3TC/EFV</th>
<th>ZDV/3TC/ABC/EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 weeks</td>
<td>26%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>144 weeks</td>
<td></td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Virologic success (48 weeks HIV RNA &lt; 50 copies/ml)</td>
<td>63%</td>
<td>80%</td>
<td>86%</td>
</tr>
</tbody>
</table>

- **Therapy naïve children**

In a 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).

- **Therapy experienced patients**

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 log₁₀ 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 (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 patients**

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{sub}10 copies/ml versus -1.83 log{sub}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.

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{sub}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 $C_{\text{max}}$ and $C_{\text{min}}$ of abacavir are approximately 3.00 $\mu$g/ml (30%) and 0.01 $\mu$g/ml (99%), respectively. The mean (CV) AUC over a dosing interval of 12 hours was 6.02 $\mu$g.h/ml (29%), equivalent to a daily AUC of approximately 12.0 $\mu$g.h/ml. The $C_{\text{max}}$ value for the oral solution is slightly higher than the tablet. After a 600 mg abacavir tablet dose, the mean (CV) abacavir $C_{\text{max}}$ was approximately 4.26 $\mu$g/ml (28%) and the mean (CV) AUC$_{\infty}$ was 11.95 $\mu$g.h/ml (21%).

Food delayed absorption and decreased $C_{\text{max}}$, 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 cerebrospinal fluid (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 $\mu$g/ml or 0.26 $\mu$M 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.

Metabolism: 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$_{24,\text{ss}}$ + 32 %, $C_{\text{max24,ss}}$ + 99 % and $C_{\text{trough24,ss}}$ + 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 populations**

*Hepatically impaired:* abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. The results showed that there was a mean 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 recommendation on
dosage reduction is possible in patients with mild hepatic impairment due to the substantial variability of abacavir exposure.

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

Children: according to clinical trials performed in children abacavir is rapidly and well absorbed from an oral solution administered to children. The overall pharmacokinetic parameters in children are comparable to adults, with greater variability in plasma concentrations. The recommended dose for children from three months to 12 years is 8 mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve therapeutic concentrations equivalent to 300 mg twice daily in adults.

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

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

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

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

Coating:
Triacetin
Methylhydroxypropylecellulose
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

Polyvinyl chloride/foil blister packs containing 60 tablets.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

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: 8 July 2004

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.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:

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

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

The oral solution is clear to slightly opalescent yellowish, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ziagen is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

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. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see “Management after an interruption of Ziagen therapy”). Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing (see section 4.4 and 4.8).

4.2 Posology and method of administration

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

Adults and adolescents: 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).

Patients changing to the once daily regimen should take 300 mg (15 ml) twice a day and switch to 600 mg (30 ml) once a day the following morning. Where an evening once daily regimen is preferred, 300 mg (15 ml) of Ziagen should be taken on the first morning only, followed by 600 mg (30 ml) in the evening. When changing back to a twice daily regimen, patients should complete the day's treatment and start 300 mg (15 ml) twice a day the following morning.
Children from three months to 12 years: the recommended dose is 8 mg/kg twice daily up to a maximum of 600 mg (30 ml) daily.

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

Ziagen can be taken with or without food.

Ziagen is also available as a tablet formulation.

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 dose recommendation can be made in patients with mild hepatic impairment. In patients with moderate hepatic impairment, no data are available, therefore the use of abacavir is not recommended unless judged necessary. If abacavir is used in patients with mild or moderate hepatic impairment, then close monitoring is required, and if feasible, monitoring of abacavir plasma levels is recommended (see section 5.2). Abacavir is contraindicated in patients with severe hepatic impairment (see section 4.3 and 4.4).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. See BOXED INFORMATION ON HYPERSENSITIVITY REACTIONS in sections 4.4. and 4.8.

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Hypersensitivity reaction (see also section 4.8):

In a clinical study, 3.4 % of subjects with a negative HLA-B*5701 status receiving abacavir developed a hypersensitivity reaction.

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. Based on the prospective study CNA106030 (PREDICT-1), use of pre-therapy screening for the HLA-B*5701 allele and subsequently avoiding abacavir in patients with this allele significantly reduced the incidence of abacavir hypersensitivity reactions. In populations similar to that enrolled in the PREDICT-1 study, it is estimated that 48% to 61% of patients with the HLA-B*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0% to 4% of patients who do not have the HLA-B*5701 allele.

These results are consistent with those of prior retrospective studies.

As a consequence, 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. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see “Management after an interruption of Ziagen therapy”). Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available based on the treatment history and resistance testing (see section 4.1).

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. It is noteworthy that among patients with a clinically suspected hypersensitivity reaction, a proportion did not carry HLA-B*5701. Therefore, even in the absence of HLA-B*5701 allele, it is important to permanently discontinue abacavir and not rechallenge
with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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

- **Clinical description**

Hypersensitivity reactions are characterised by the appearance of symptoms indicating multi-organ system involvement. Almost all hypersensitivity reactions will have fever and/or rash as part of the syndrome.

Other signs and symptoms may include respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised), gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and may lead to misdiagnosis of hypersensitivity as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis. Other frequently observed signs or symptoms of the hypersensitivity reaction may include lethargy or malaise and musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia).

The symptoms related to this hypersensitivity reaction worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of Ziagen.

- **Clinical management**

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

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

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

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, Ziagen must be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications).

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

- **Management after an interruption of Ziagen therapy**

Regardless of a patient’s HLA-B*5701 status, if therapy with Ziagen has been discontinued for any reason and restarting therapy is under consideration, the reason for discontinuation must be established to assess whether the patient had any symptoms of a hypersensitivity reaction. If a hypersensitivity reaction cannot be ruled out, Ziagen or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir) must not be restarted.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred
after restarting Ziagen in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping Ziagen. The most common isolated symptom of a hypersensitivity reaction was a skin rash. Moreover, on very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction (i.e. patients previously considered to be abacavir tolerant). In both cases, if a decision is made to restart Ziagen this must be done in a setting where medical assistance is readily available.

Screening for carriage of the HLA B*5701 allele is recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Re-initiation of abacavir in such patients who test positive for the HLA B*5701 allele is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and with close medical supervision.

**Essential patient information**

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

- patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.

- patients must also be informed that a HLA-B*5701 negative patient can also experience an abacavir hypersensitivity reaction. Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT THEIR DOCTOR IMMEDIATELY.

- patients who are hypersensitive to abacavir should be reminded that they must never take Ziagen or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir) again, regardless of their HLA-B*5701 status.

- in order to avoid restarting Ziagen, patients who have experienced a hypersensitivity reaction should be asked to return the remaining Ziagen tablets or oral solution to the pharmacy.

- patients who have stopped Ziagen for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.

- each patient should be reminded to read the Package Leaflet included in the Ziagen pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

**Lactic acidosis**: lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.
Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

**Mitochondrial dysfunction:** nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

**Lipodystrophy:** combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

**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 contraindicated in patients with severe hepatic impairment (see section 4.3). 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.

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.

A pharmacokinetic study has been performed in patients with mild hepatic impairment. However, a definitive recommendation on dose reduction is not possible due to substantial variability of drug exposure in this patient population (see section 5.2). The clinical safety data available with abacavir in hepatically impaired patients is very limited. Due to the potential increases in exposure (AUC) in some patients, close monitoring is required. No data are available in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to substantially increase in these
patients. Therefore, the use of abacavir in patients with moderate hepatic impairment is not recommended unless judged necessary and requires close monitoring of these patients.

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).

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.

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

Opportunistic infections: patients receiving Ziagen or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission: patients should be advised that current antiretroviral therapy, including Ziagen, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

Mycoardial 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 try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

4.5 Interaction with other medicinal products and other forms of interaction

Based on the results of in vitro experiments and the known major metabolic pathways of abacavir, the potential for P450 mediated interactions with other medicinal products involving abacavir is low. P450 does not play a major role in the metabolism of abacavir, and abacavir does not inhibit metabolism mediated by CYP 3A4. Abacavir has also been shown in vitro not to inhibit CYP 3A4, 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 Cmax and a one hour delay in tmax 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.

4.6 Pregnancy and lactation

Ziagen is not recommended during pregnancy. The safe use of abacavir in human pregnancy has not been established. Placental transfer of abacavir and/or its related metabolites has been shown to occur in animals. Toxicity to the developing embryo and foetus occurred in rats, but not in rabbits (see section 5.3). The teratogenic potential of abacavir could not be established from studies in animals.

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

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

<table>
<thead>
<tr>
<th>Hypersensitivity (see also section 4.4):</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a clinical study, 3.4 % of subjects with a negative HLA-B*5701 status receiving abacavir developed a hypersensitivity reaction. In clinical studies with abacavir 600 mg once daily the reported rate of hypersensitivity remained within the range recorded for abacavir 300 mg twice daily.</td>
</tr>
</tbody>
</table>

Some hypersensitivity reactions were life-threatening and resulted in fatal outcome despite taking precautions. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

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

The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in at least 10% of patients
with a hypersensitivity reaction are in bold text.

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

Rash (81% vs 67% respectively) and gastrointestinal manifestations (70% vs 54% respectively) were more frequently reported in children compared to adults.

Some patients with hypersensitivity reactions were initially thought to have gastroenteritis, respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. This delay in diagnosis of hypersensitivity has resulted in Ziagen being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases.

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. Close medical supervision is necessary during the first two months, with consultations every two weeks.

It is likely that intermittent therapy may increase the risk of developing sensitisation and therefore occurrence of clinically significant hypersensitivity reactions. Consequently, patients should be advised of the importance of taking Ziagen regularly.

Restarting Ziagen following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction is usually more severe than on initial presentation, and may include life-threatening hypotension and death. **Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue Ziagen and must never be rechallenged with Ziagen, or any other medicinal product containing abacavir (e.g. Kivexa, Trizivir).**

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, Ziagen must be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications).

**Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after restarting Ziagen in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping Ziagen. The most common isolated symptom of a hypersensitivity reaction was a skin rash. Moreover, on very rare occasions hypersensitivity reactions have been reported in patients who have restarted therapy and who had no preceding symptoms of a hypersensitivity**
reaction. In both cases, if a decision is made to restart Ziagen this must be done in a setting where medical assistance is readily available.

Each patient must be warned about this hypersensitivity reaction to abacavir.

For many of the other 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 those 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 reaction. If Ziagen has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart a medicinal product containing abacavir, this must be done in a setting where medical assistance is readily available (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

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

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

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

Laboratory abnormalities
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.

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. Abacavir shows synergy in vitro in combination with nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, lamivudine and stavudine.

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 EC₅₀ 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%).
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Abacavir +</th>
<th>Abacavir +</th>
<th>Abacavir +</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Combivir²</td>
<td>lamivudine +</td>
<td>lamivudine +</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NNRTI</td>
<td>PI (or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PI/ritonavir</td>
<td></td>
</tr>
<tr>
<td>Number of Subjects</td>
<td>282</td>
<td>1094</td>
<td>909</td>
<td>2285</td>
</tr>
<tr>
<td>Number of Virological Failures</td>
<td>43</td>
<td>90</td>
<td>158</td>
<td>306</td>
</tr>
<tr>
<td>Number of On-Therapy Genotypes</td>
<td>40 (100%)</td>
<td>51 (100%)²</td>
<td>141 (100%)</td>
<td>232 (100%)</td>
</tr>
<tr>
<td>K65R</td>
<td>0</td>
<td>1 (2%)</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>L74V</td>
<td>0</td>
<td>9 (18%)</td>
<td>3 (2%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Y115F</td>
<td>0</td>
<td>2 (4%)</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>M184V/I</td>
<td>34 (85%)</td>
<td>22 (43%)</td>
<td>70 (50%)</td>
<td>126 (54%)</td>
</tr>
<tr>
<td>TAMs³</td>
<td>3 (8%)</td>
<td>2 (4%)</td>
<td>4 (3%)</td>
<td>9 (4%)</td>
</tr>
</tbody>
</table>

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≤0.012). 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.
<table>
<thead>
<tr>
<th>Baseline Reverse Transcriptase Mutation</th>
<th>Week 4 (n = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>None</td>
<td>15</td>
</tr>
<tr>
<td>M184V alone</td>
<td>75</td>
</tr>
<tr>
<td>Any one NRTI mutation</td>
<td>82</td>
</tr>
<tr>
<td>Any two NRTI-associated mutations</td>
<td>22</td>
</tr>
<tr>
<td>Any three NRTI-associated mutations</td>
<td>19</td>
</tr>
<tr>
<td>Four or more NRTI-associated mutations</td>
<td>28</td>
</tr>
</tbody>
</table>

**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 Experience**

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.
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.

<table>
<thead>
<tr>
<th></th>
<th>ZDV/3TC/ABC</th>
<th>ZDV/3TC/EFV</th>
<th>ZDV/3TC/ABC/EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure (HIV RNA &gt;200 copies/ml)</td>
<td>32 weeks 26%</td>
<td>144 weeks -</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>16%</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Virologic success (48 weeks HIV RNA &lt; 50 copies/ml)</td>
<td>63%</td>
<td>80%</td>
<td>86%</td>
</tr>
</tbody>
</table>

- **Therapy naïve children**

In a 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).

- **Therapy experienced patients**

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 (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 patients**

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.

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 $C_{\text{max}}$ and $C_{\text{min}}$ of abacavir are approximately 3.00 $\mu$g/ml (30%) and 0.01 $\mu$g/ml (99%), respectively. The mean (CV) AUC over a dosing interval of 12 hours was 6.02 $\mu$g.h/ml (29%), equivalent to a daily AUC of approximately 12.0 $\mu$g.h/ml. The $C_{\text{max}}$ value for the oral solution is slightly higher than the tablet. After a 600 mg abacavir tablet dose, the mean (CV) abacavir $C_{\text{max}}$ was approximately 4.26 $\mu$g/ml (28%) and the mean (CV) $AUC_{\infty}$ was 11.95 $\mu$g.h/ml (21%).

Food delayed absorption and decreased $C_{\text{max}}$ 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 cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%. The observed values of the peak concentrations are 9% greater than the IC$_{50}$ of abacavir of 0.08 $\mu$g/ml or 0.26 $\mu$M 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.

**Metabolism:** 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 %, $C_{\text{max}}$ + 99 % and $C_{\text{trough}}$ + 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 populations**

*Hepatically impaired:* abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) receiving a single 600 mg dose. The results showed that there was a mean 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 recommendation on dosage reduction is possible in patients with mild hepatic impairment due to the substantial variability of abacavir exposure.
Renally impaired: abacavir is primarily metabolised by the liver with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment. Based on limited experience Ziagen should be avoided in patients with end-stage renal disease.

Children: according to clinical trials performed in children abacavir is rapidly and well absorbed from an oral solution administered to children. The overall pharmacokinetic parameters in children are comparable to adults, with greater variability in plasma concentrations. The recommended dose for children from three months to 12 years is 8 mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve therapeutic concentrations equivalent to 300 mg twice daily in adults.

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

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

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  
Natural and 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.  
A 10 ml polypropylene oral dosing syringe and a polyethylene adapter are also included in the pack.

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 UK Limited  
980 Great West Road  
Brentford  
Middlesex  
TW8 9GS  
United Kingdom
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: 8 July 2004

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

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

Film-coated Tablets

Glaxo Operations UK Ltd
(trading as Glaxo Wellcome Operations)
Priory Street
Ware
Herts SG12 0DJ
United Kingdom

or

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

Oral Solution

Glaxo Wellcome GmbH & Co. KG
Industriestrasse 32-36
23843 Bad Oldesloe
Germany

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 OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

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

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

• OTHER CONDITIONS

Pharmacovigilance System
The MAH must ensure that the system of pharmacovigilance, as described in version 7.2 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 03 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.
As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

The Marketing Authorisation Holder will submit Periodic Safety Update Reports and other safety information annually.
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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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)
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) 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).

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 UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

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
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLET BLISTER FOIL TEXT</td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Ziagen 300 mg tablets.</td>
</tr>
<tr>
<td>Abacavir</td>
</tr>
<tr>
<td>2. NAME OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td>ViiV Healthcare UK Limited</td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP {MM/YYYY}</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td>5. OTHER</td>
</tr>
</tbody>
</table>
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 REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight 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)
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) 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).

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 UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

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
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**HYPERSENSITIVITY REACTION**

Patients taking Ziagen may develop a hypersensitivity reaction (serious allergic reaction) which can be life-threatening if treatment with Ziagen is continued. It is essential you read the information on this reaction under “Take special care with Ziagen” in section 2 of this leaflet. There is also an Alert Card included in the Ziagen pack, to remind you and medical staff about Ziagen hypersensitivity. This card should be removed and kept with you at all times.

**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 a hypersensitivity reaction, YOU MUST NEVER TAKE Ziagen, or any other medicine containing abacavir (i.e. Kivexa, Trizivir) again, as within hours you may experience a life-threatening lowering of your blood pressure or death.

In this leaflet:
1. What Ziagen is and what it is used for
2. Before you take Ziagen
3. How to take Ziagen
4. Possible side effects
5. How to store Ziagen
6. Further information

1. WHAT ZIAGEN IS AND WHAT IT IS USED FOR

Ziagen belongs to a group of antiviral medicines, also known as antiretrovirals, called nucleoside analogue reverse transcriptase inhibitors (NRTIs). These are used to treat Human Immunodeficiency Virus (HIV) infection.

Ziagen is used in combination with other antiretroviral medicines for the treatment of HIV infection. It reduces HIV viral load, and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cell that play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Ziagen varies between patients. Your doctor will be monitoring the effectiveness of your treatment.
2. BEFORE YOU TAKE ZIAGEN

Do not take Ziagen:

- if you are allergic (hypersensitive) to the active substance abacavir, which is also included in medicines called Kivexa and Trizivir.
- if you are allergic to any of the other ingredients in Ziagen
- if you have severe liver disease.

If you are not sure about any of these please consult your doctor.

Take special care with Ziagen

**Hypersensitivity reaction (serious allergic reaction):** About 3 to 4 in every 100 patients treated with abacavir in a clinical trial who did not have a gene called HLA-B*5701 developed a hypersensitivity reaction. Research has found that people with the gene HLA-B*5701 are more likely to have a hypersensitivity reaction to abacavir. However, even if you do not have this gene type, it is possible for you to get this reaction, which could be life-threatening if you continue to take Ziagen. If you know you have this gene type, be sure to tell your doctor before you take abacavir.

The most common symptoms of this reaction are high temperature (fever) and a skin rash. Other frequently observed signs are nausea, vomiting, diarrhoea, abdominal pain and severe tiredness. Other symptoms may include joint or muscle pain, swelling of the neck, shortness of breath, sore throat, cough and headache. Occasionally inflammation of the eye (conjunctivitis), mouth ulcers or low blood pressure may occur.

The symptoms of this allergic reaction can occur at any time during treatment with Ziagen. However they usually occur in the first six weeks of treatment. The symptoms worsen with continued treatment and may be life-threatening if treatment is continued.

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 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 a hypersensitivity reaction, **YOU MUST NEVER TAKE** Ziagen or any other medicine containing abacavir (i.e. Kivexa, Trizivir) again, as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

If you have stopped taking Ziagen for any reason, particularly because you think you are having side effects or for other illness, it is important that you contact your doctor before restarting. Your doctor will check whether any symptoms you had may be related to this hypersensitivity reaction. If your doctor thinks there is a possibility that they were related, you will be instructed **never to take Ziagen or any other medicine containing abacavir (i.e. Kivexa, Trizivir) again.** It is important that you follow this advice.
Occasionally life-threatening hypersensitivity reactions have occurred when Ziagen was restarted in patients who reported only one of the symptoms on the Alert Card before stopping.

On very rare occasions hypersensitivity has been reported when Ziagen was restarted in patients who had no symptoms of hypersensitivity before stopping.

If you are hypersensitive to Ziagen you should return all of your unused Ziagen for disposal. Ask your doctor or pharmacist for advice.

*Lactic acidosis:* the class of medicines to which Ziagen belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Deep, rapid breathing, drowsiness, and non specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. This rare, but serious side effect occurs more often in women, particularly if very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Ziagen, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

*Fat distribution:* redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

*Liver disease/hepatitis:* please tell your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk of severe and potentially fatal liver adverse events and may require blood tests for monitoring of liver function.

If you have liver disease you may get higher amounts of abacavir in your blood, compared to people with a healthy liver. Patients with liver disease being treated with Ziagen will be monitored closely for side effects, which may occur more frequently with higher doses of abacavir. Ziagen is not recommended if you have moderate liver disease. Discuss this with your doctor if you are unsure.

*Pancreatitis:* inflammation of the pancreas (pancreatitis) has been reported in some patients taking Ziagen. However it is not certain whether this is caused by Ziagen, other medications you may be taking or your HIV infection.

*Immune Reactivation Syndrome:* In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

*Bone problems:* Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

*Heart attack:* It cannot be excluded that abacavir might be associated with an increased risk of heart attack. If you have heart problems, smoke or suffer from diseases that increase your risk of heart disease such as high blood pressure and diabetes, tell your doctor. Do not stop taking your medication unless you are advised to do so by your doctor.
**General:** Ziagen helps to control your condition but is not a cure for HIV infection. You will need to take it every day. Do not interrupt your medication without first talking to your doctor. If however, you suspect you are developing a hypersensitivity reaction contact your doctor immediately who will advise you whether you should stop taking Ziagen.

Treatment with Ziagen has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.

You may continue to develop other infections and other illnesses associated with HIV disease. You should therefore keep in regular contact with your doctor while taking Ziagen.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Ziagen is unlikely to significantly interact with other medicines you are being treated with.

Alcohol does increase the amount of abacavir in your blood. If you are taking oral vitamin A related medicines, e.g. isotretinoin, you should inform your doctor, since these may also increase the amount of abacavir in your blood. As abacavir increases the rate at which methadone is removed from the body, patients taking methadone will be checked for any withdrawal symptoms, and may have their methadone dose changed.

**Taking Ziagen with food and drink**
Ziagen can be taken with food or on an empty stomach.

**Pregnancy and breast-feeding**
Ziagen is not recommended for use during pregnancy. If you become pregnant, or are planning to become pregnant, you must contact your doctor to discuss the potential adverse effects and the benefits and risks of your antiretroviral therapy to you and your child.

If you have taken Ziagen during your pregnancy, your doctor may request regular visits to monitor the development of your child. Such visits may include blood tests and other diagnostic tests.

In children whose mother took nucleoside and nucleotide analogues during pregnancy, the benefit from the reduced chance of being infected with HIV is greater than the risk of suffering from side effects.

The active substance abacavir in this medicine is likely to be found in human breast milk. There are no safety data available following treatment with Ziagen in babies under three months of age. You are therefore recommended not to breast-feed your baby while taking Ziagen. Additionally, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV from mother to child. If you are breast-feeding you must inform your doctor.

**Driving and using machines**
No studies on the effects of Ziagen on the ability to drive and use machines have been performed. However, you should take into account the state of your health and the possible side effects of Ziagen before considering driving or using machines.

3. **HOW TO TAKE ZIAGEN**
Always take Ziagen exactly as your doctor has told you, and take great care not to miss any doses if at all possible. You should check with your doctor or pharmacist if you are not sure.

The usual daily dose of Ziagen in adults and adolescents over 12 years of age is 600 mg. This can be taken either as one 300 mg tablet twice a day approximately 12 hours apart or two 300 mg tablets once a day.
In children three months to 12 years of age the dose given depends on the body weight of your child. The recommended dose is:

Children weighing at least 30 kg should take the adult dose of one tablet twice daily.

Children weighing more than 21 kg to less than 30 kg: one-half of a Ziagen tablet taken in the morning and one whole tablet taken in the evening.

Children weighing 14 to 21 kg: one-half of a Ziagen tablet twice daily.

Swallow the tablet(s) with water. Ziagen can be taken with or without food.

An oral solution (20 mg abacavir/ml) is also available for the treatment of children over three months and weighing less than 14 kg and patients who require a reduction in the usual dose or for patients unable to take tablets.

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.

**If you take more Ziagen than you should**
If you accidentally take too much of your medicine you should 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 of your medicine, take it as soon as you remember, and then continue as before. Do not take a double dose to make up for a forgotten dose. It is important to take Ziagen regularly because irregular intake may increase the risk of hypersensitivity reactions.

**If you stop taking Ziagen**
If you have stopped taking Ziagen for any reason, particularly because you think you are having side effects or for other illness, it is important that you contact your doctor before restarting. In some cases your doctor will ask you to restart Ziagen in a place where you will be able to get ready access to medical care if needed.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Ziagen can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by Ziagen, by other medicines you are taking at the same time or by the HIV disease. For this reason it is very important that you inform your doctor about any changes in your health.

**About 3 to 4 in every 100 patients treated with abacavir in a clinical trial who did not have a gene called HLA-B*5701 developed a hypersensitivity reaction (serious allergic reaction).** This is described under “Take special care with Ziagen” in section 2 of this leaflet. It is important that you read and understand the information about this serious reaction.

**Common side effects (reported in 1 to 10 out of 100 patients):**
- skin rash (without any other illness)
- nausea, vomiting, diarrhoea,
- headache,
- high temperature,
- lethargy, fatigue, loss of appetite

**Rare side effects (reported in less than 1 in 1000 patients):**
- inflammation of the pancreas (pancreatitis).
Very rare side effects (reported in less than 1 in 10,000 patients):
-serious skin reactions

Cases of a condition called lactic acidosis, which is a build up of lactic acid in the body, that can cause dehydration and coma have been reported on rare occasions in patients taking NRTIs (see "Take special care with Ziagen" under section 2 for more information).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump'). The cause and long-term health effects of these conditions are not known at this time.

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ZIAGEN

Keep out of the reach and sight of children.

Do not use Ziagen after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Do not store above 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ziagen contains

Each Ziagen film-coated tablet contains 300 mg of the active ingredient abacavir (as sulfate). The tablet core contains microcrystalline cellulose, sodium starch glycollate, magnesium stearate and colloidal anhydrous silica. The tablet coating contains triacetin, methylhydroxypropylecellulose, titanium dioxide, polysorbate 80 and iron oxide yellow.

What Ziagen looks like and contents of the pack

The film-coated, scored capsule shaped tablets are yellow and engraved with ‘GX 623’ on both sides. They are provided in blister packs containing 60 tablets.
Marketing Authorisation Holder and Manufacturer(s)

Manufacturer

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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu
Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

HYPERSENSITIVITY REACTION

Patients taking Ziagen may develop a hypersensitivity reaction (serious allergic reaction) which can be life-threatening if treatment with Ziagen is continued. It is essential you read the information on this reaction under “Take special care with Ziagen” in section 2 of this leaflet. There is also an Alert Card included in the Ziagen pack, to remind you and medical staff about Ziagen hypersensitivity. This card should be removed and kept with you at all times.

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 a hypersensitivity reaction, YOU MUST NEVER TAKE Ziagen, or any other medicine containing abacavir (i.e. Kivexa, Trizivir) again, as within hours you may experience a life-threatening lowering of your blood pressure or death.

In this leaflet:
1. What Ziagen is and what it is used for
2. Before you take Ziagen
3. How to take Ziagen
4. Possible side effects
5. How to store Ziagen
6. Further information

1. WHAT ZIAGEN IS AND WHAT IT IS USED FOR

Ziagen belongs to a group of antiviral medicines, also known as antiretrovirals, called nucleoside analogue reverse transcriptase inhibitors (NRTIs). These are used to treat Human Immunodeficiency Virus (HIV) infection.

Ziagen is used in combination with other antiretroviral medicines for the treatment of HIV infection. It reduces HIV viral load, and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cell that play an important role in maintaining a healthy immune system to help fight infection. Response to treatment with Ziagen varies between patients. Your doctor will be monitoring the effectiveness of your treatment.
2. **BEFORE YOU TAKE ZIAGEN**

**Do not take Ziagen:**
- if you are allergic (hypersensitive) to the active substance abacavir, which is also included in medicines called Kivexa and Trizivir.
- if you are allergic to any of the other ingredients in Ziagen
- if you have severe liver disease

If you are not sure about any of these please consult your doctor.

**Take special care with Ziagen**

**Hypersensitivity reaction (serious allergic reaction):** About 3 to 4 in every 100 patients treated with abacavir in a clinical trial who did not have a gene called HLA-B*5701 developed a hypersensitivity reaction. Research has found that people with the gene HLA-B*5701 are more likely to have a hypersensitivity reaction to abacavir. However, even if you do not have this gene type, it is possible for you to get this reaction, which could be life-threatening if you continue to take Ziagen. If you know you have this gene type, be sure to tell your doctor before you take abacavir.

The most common symptoms of this reaction are high temperature (fever) and a skin rash. Other frequently observed signs or symptoms include nausea, vomiting, diarrhoea, abdominal pain and severe tiredness. Other symptoms may include joint or muscle pain, swelling of the neck, shortness of breath, sore throat, cough and headache. Occasionally inflammation of the eye (conjunctivitis), mouth ulcers or low blood pressure may occur.

The symptoms of this allergic reaction can occur at any time during treatment with Ziagen. However, they usually occur in the first six weeks of treatment. The symptoms worsen with continued treatment and may be life-threatening if treatment is continued.

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 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 a hypersensitivity reaction, **YOU MUST NEVER TAKE Ziagen or any other medicine containing abacavir (i.e. Kivexa, Trizivir) again, as within hours you may experience a life-threatening lowering of your blood pressure or death.**

If you have stopped taking Ziagen for any reason, particularly because you think you are having side effects or for other illness, it is important that you contact your doctor before restarting. Your doctor will check whether any symptoms you had may be related to this hypersensitivity reaction. If your doctor thinks there is a possibility that they were related, you will be instructed **never to take Ziagen or any other medicine containing abacavir (i.e. Kivexa, Trizivir) again.** It is important that you follow this advice.

Occasionally life-threatening hypersensitivity reactions have occurred when Ziagen was restarted in patients who reported **only one** of the symptoms on the Alert Card before stopping.

On very rare occasions hypersensitivity has been reported when Ziagen was restarted in patients who
had no symptoms of hypersensitivity before stopping.

If you are hypersensitive to Ziagen you should return all of your unused Ziagen for disposal. Ask your doctor or pharmacist for advice.

*Lactic acidosis:* the class of medicines to which Ziagen belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Deep, rapid breathing, drowsiness, and non specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. This rare, but serious side effect occurs more often in women, particularly if very overweight. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with Ziagen, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

*Fat distribution:* redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

*Liver disease/hepatitis:* please tell your doctor if you have a history of liver disease. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk of severe and potentially fatal liver adverse events and may require blood tests for monitoring of liver function.

If you have liver disease you may get higher amounts of abacavir in your blood, compared to people with a healthy liver. Patients with liver disease being treated with Ziagen will be monitored closely for side effects, which may occur more frequently with higher doses of abacavir. Ziagen is not recommended if you have moderate liver disease. Discuss this with your doctor if you are unsure.

*Pancreatitis:* inflammation of the pancreas (pancreatitis) has been reported in some patients taking Ziagen. However it is not certain whether this is caused by Ziagen, other medications you may be taking or your HIV infection.

*Immune Reactivation Syndrome:* In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body’s immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

*Bone problems:* Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

*Heart attack:* It cannot be excluded that abacavir might be associated with an increased risk of heart attack. If you have heart problems, smoke or suffer from diseases that increase your risk of heart disease such as high blood pressure and diabetes, tell your doctor. Do not stop taking your medication unless you are advised to do so by your doctor.

*General:* Ziagen helps to control your condition but is not a cure for HIV infection. You will need to take it every day. Do not interrupt your medication without first talking to your doctor. If however, you suspect you are developing a hypersensitivity reaction contact your doctor immediately who will advise you whether you should stop taking Ziagen.

Treatment with Ziagen has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.
You may continue to develop other infections and other illnesses associated with HIV disease. You should therefore keep in regular contact with your doctor while taking Ziagen.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Ziagen is unlikely to significantly interact with other medicines you are being treated with.

Alcohol does increase the amount of abacavir in your blood. If you are taking oral vitamin A related medicines, e.g. isotretinoin, you should inform your doctor, since these may also increase the amount of abacavir in your blood. As abacavir increases the rate at which methadone is removed from the body, patients taking methadone will be checked for any withdrawal symptoms, and may have their methadone dose changed.

**Taking Ziagen with food and drink**
Ziagen can be taken with food or on an empty stomach.

**Pregnancy and breast-feeding**
Ziagen is not recommended for use during pregnancy. If you become pregnant, or are planning to become pregnant, you must contact your doctor to discuss the potential adverse effects and the benefits and risks of your antiretroviral therapy to you and your child.

If you have taken Ziagen during your pregnancy, your doctor may request regular visits to monitor the development of your child. Such visits may include blood tests and other diagnostic tests.

In children whose mother took nucleoside and nucleotide analogues during pregnancy, the benefit from the reduced chance of being infected with HIV is greater than the risk of suffering from side effects.

The active substance abacavir in this medicine is likely to be found in human breast milk. There are no safety data available following treatment with Ziagen in babies under three months of age. You are therefore recommended not to breast-feed your baby while taking Ziagen. Additionally, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV from mother to child. If you are breast-feeding you must inform your doctor.

**Driving and using machines**
No studies on the effects of Ziagen on the ability to drive and use machines have been performed. However, you should take into account the state of your health and the possible side effects of Ziagen before considering driving or using machines.

**Important information about some of the other ingredients of Ziagen oral solution**
This medicine contains the sweetener sorbitol (approximately 5 g in each 15 ml dose), which may have a mild laxative effect. Medicines containing sorbitol should not be taken if you have hereditary fructose intolerance. 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).

3. **HOW TO TAKE ZIAGEN**
Always take Ziagen exactly as your doctor has told you, and take great care not to miss any doses if at all possible. You should check with your doctor or pharmacist if you are not sure.
The usual daily dose of Ziagen in adults and adolescents over 12 years of age is 600 mg (30 ml). This can be taken either as 300 mg (15 ml) twice a day approximately 12 hours apart or 600 mg (30 ml) once a day. Ziagen does not have to be taken with food.

In children three months to 12 years of age the dose given depends on the body weight of your child. The recommended dose is 8 mg/kg twice a day up to a maximum of 600 mg daily.

Use the oral dosing syringe supplied with the pack to measure your dose accurately.

1. Remove the bottle cap.
2. Push the plastic adapter into the neck of the bottle, while holding the bottle firmly.
3. Insert the syringe firmly into the adapter.
4. Turn bottle upside down.
5. Pull out syringe plunger until the correct amount is withdrawn.
6. Turn the bottle the correct way up and remove the syringe from the adapter.
7. Replace and tighten the bottle cap.
8. Administer the dose into the mouth by placing the tip of the syringe against the inside of the cheek. Slowly depress the plunger, allowing time to swallow. Forceful squirting to the back of the throat may cause choking.

After use the syringe must not be left in the bottle and should be washed thoroughly in clean water.

If you take more Ziagen than you should
If you accidentally take too much of your medicine you should 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 of your medicine, take it as soon as you remember, and then continue as before. Do not take a double dose to make up for forgotten individual doses. It is important to take Ziagen regularly because irregular intake may increase the risk of hypersensitivity reactions.

If you stop taking Ziagen
If you have stopped taking Ziagen for any reason, particularly because you think you are having side effects or for other illness, it is important that you contact your doctor before restarting. In some cases your doctor will ask you to restart Ziagen in a place where you will be able to get ready access to medical care if needed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ziagen can cause side effects although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by Ziagen, by other medicines you are taking at the same time or by the HIV disease. For this reason it is very important that you inform your doctor about any changes in your health.

About 3 to 4 in every 100 patients treated with abacavir in a clinical trial who did not have a gene called HLA-B*5701 developed a hypersensitivity reaction (serious allergic reaction). This is described under “Take special care with Ziagen” in section 2 of this leaflet. It is important that you read and understand the information about this serious reaction.

Common side effects (reported in 1 to 10 out of 100 patients):
- skin rash (without any other illness)
- nausea, vomiting, diarrhoea,
- headache,
- high temperature,
- lethargy, fatigue, loss of appetite

Rare side effects (reported in less than 1 in 1000 patients):
-inflammation of the pancreas (pancreatitis).

**Very rare side effects (reported in less than 1 in 10,000 patients):**
- serious skin reactions

Cases of a condition called lactic acidosis, which is a build up of lactic acid in the body, that can cause dehydration and coma have been reported on rare occasions in patients taking NRTIs (see “Take special care with Ziagen” in section 2 for more information).

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time.

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE ZIAGEN**

Keep out of the reach and sight of children.

Do not store above 30°C.

Discard oral solution two months after first opening.

Do not use Ziagen after the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What Ziagen contains**

Ziagen oral solution contains 20 mg of the active ingredient abacavir (as sulfate) in each ml of the solution.

Other ingredients: Sorbitol 70% (E420), saccharin sodium, sodium citrate, citric acid anhydrous, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), propylene glycol (E1520), maltodextrin, lactic acid, glyceryl triacetate, natural and artificial strawberry and banana flavour, purified water.

**What Ziagen looks like and contents of the pack**

Ziagen oral solution is clear to yellowish in colour 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 is included in the pack.
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