

# DATA SHEET

## **KIVEXA<sup>®</sup> Film Coated Tablet.**

***Abacavir + Lamivudine fixed dose combination***

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### **Presentation**

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Film-coated tablets.

Orange, film-coated, modified capsule shaped tablets, debossed with GS FC2 on one side. Do not halve tablets.

Each film-coated tablet contains 600mg of abacavir as abacavir sulfate and 300mg lamivudine.

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### **Uses**

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#### ***Actions***

#### **Pharmacotherapeutic group**

Nucleoside reverse transcriptase inhibitor (NRTI) – ATC Code: J05A F30.

#### **Mechanism of action**

Abacavir and lamivudine are NRTIs, and are potent, selective inhibitors of HIV-1 and HIV-2. Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective triphosphate (TP) which are the active moieties. Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

In a study of 20 HIV-infected patients receiving abacavir 300mg twice daily, with only one 300mg dose taken prior to the 24h sampling period, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6h, compared to the geometric mean abacavir plasma half-life in this study of 2.6h. The steady state pharmacokinetic properties of abacavir 600 mg once daily was compared to abacavir 300 mg twice daily in a crossover study in 27 HIV-infected patients. Intracellular carbovir triphosphate exposures in peripheral blood mononuclear cells were higher for abacavir 600 mg once daily with respect to AUC<sub>24,ss</sub> (32 %, higher), C<sub>max 24,ss</sub> (99% higher) and trough values (18% higher), compared to the 300 mg twice daily regimen. For

patients receiving lamivudine 300mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16 to 19h, compared to the plasma lamivudine half-life of 5 to 7h. The steady state pharmacokinetic properties of lamivudine 300 mg once daily for 7 days compared to lamivudine 150 mg twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were similar with respect to  $AUC_{24,ss}$  and  $C_{max\ 24,ss}$ ; however, trough values were lower compared to the 150 mg twice daily regimen. Inter subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. These data support the use of lamivudine 300mg and abacavir 600mg once daily for the treatment of HIV-infected patients. Additionally, the efficacy and safety of this combination given once daily has been demonstrated in a pivotal clinical study (CNA30021- see *Clinical Studies*).

### **Pharmacodynamic Effects**

Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Abacavir shows synergy *in vitro* in combination with amprenavir, nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, zalcitabine, stavudine and lamivudine.

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral RT. This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. Studies *in vitro* indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the RT codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo*, requiring multiple mutations to reach an eight-fold increase in  $IC_{50}$  over wild-type virus, which may be a clinically relevant level. Isolates resistant to abacavir might also show reduced sensitivity to lamivudine, zalcitabine, tenofovir, emtricitabine and/or didanosine, but remain sensitive to zidovudine and stavudine.

Cross-resistance between abacavir or lamivudine and antiretrovirals from other classes e.g. protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI), is unlikely. Reduced 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.

Clinical isolates with three or more mutations associated with NRTIs are unlikely to be susceptible to abacavir. Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine, stavudine, abacavir and tenofovir maintain their

antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation.

### **Pharmacokinetics**

The KIVEXA tablet has been shown to be bioequivalent to abacavir and lamivudine administered separately. This was demonstrated in a single dose, 3-way crossover bioequivalence study of KIVEXA (fasted) versus 2 x 300mg abacavir tablets plus 2 x 150mg lamivudine tablets (fasted) versus KIVEXA administered with a high fat meal, in healthy volunteers (n=30).

In the fasted state there was no significant difference in the extent of absorption, as measured by the area under the plasma concentration-time curve (AUC) and maximal peak concentration ( $C_{max}$ ), of each component. There was also no clinically significant food effect observed between administration of KIVEXA in the fasted or fed state. These results indicate that KIVEXA can be taken with or without food.

The pharmacokinetic properties of lamivudine and abacavir are described below.

#### **Absorption**

Abacavir and lamivudine are rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is 83% and 80 to 85% respectively. The mean time to maximal serum concentrations ( $t_{max}$ ) is about 1.5h and 1.0h for abacavir and lamivudine respectively. Following a single oral dose of 600mg of abacavir, the mean  $C_{max}$  is 4.26micrograms/mL and the mean  $AUC_{\infty}$  is 11.95micrograms.h/mL. Following multiple-dose oral administration of lamivudine 300mg once daily for seven days the mean steady-state  $C_{max}$  is 2.04micrograms/mL and the mean  $AUC_{24}$  is 8.87micrograms.h/mL.

#### **Distribution**

Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0.8 and 1.3L/kg respectively. Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~49%) to human plasma proteins at therapeutic concentrations. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays low plasma protein binding (less than 36%). This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement.

Data show that abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). Studies with abacavir demonstrate 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 0.08micrograms/mL or 0.26micromolar when abacavir is given at 600mg twice daily. The mean ratio of CSF/serum lamivudine concentrations 2 to 4h after oral administration was approximately 12%. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

## **Metabolism**

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

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions with lamivudine is low due to the small extent of hepatic metabolism (less than 10%).

## **Elimination**

The mean half-life of abacavir is about 1.5h. Following multiple oral doses of abacavir 300mg 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.

The observed lamivudine half-life of elimination is 5 to 7h. The mean systemic clearance of lamivudine is approximately 0.32L/h/kg, predominantly by renal clearance (greater than 70%) via the organic cationic transport system.

## **Special Patient Populations**

*Hepatically impaired* - Pharmacokinetic data has been obtained for abacavir and lamivudine alone. Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). The results showed that there was a mean increase of 1.89 fold in the abacavir AUC and 1.58 fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased.

Dosage reduction of abacavir is likely to be required in patients with mild hepatic impairment. The separate preparation of abacavir (*ZIAGEN*) should therefore be used to treat these patients. The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to be variable and substantially increased in these patients. *KIVEXA* is therefore contraindicated in patients with moderate and severe hepatic impairment.

Data obtained for lamivudine in patients with moderate to severe hepatic impairment show that the pharmacokinetics are not significantly affected by hepatic dysfunction.

*Renally impaired* - Pharmacokinetic data have been obtained for abacavir and lamivudine alone. 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. Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Dose reduction is required for patients with creatinine clearance of less than 50mL/min, therefore the separate preparation of lamivudine (3TC) should be used to treat these patients.

### **Indications**

KIVEXA is a combination of two nucleoside analogues (abacavir and lamivudine). It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age.

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## **Dosage and Administration**

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

KIVEXA should not be administered to adults or adolescents who weigh less than 40kg because it is a fixed-dose tablet that cannot be dose reduced.

KIVEXA can be taken with or without food. Do not halve tablet.

KIVEXA is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance less than 50mL/min or with mild hepatic impairment. Separate preparations of abacavir (ZIAGEN™) or lamivudine (3TC™) should be administered in cases where discontinuation or dose adjustment is indicated. In these cases the physician should refer to the individual product information for these medicinal products.

### **Populations**

#### **Adults and adolescents**

The recommended dose of KIVEXA in adults and adolescents is one tablet once daily.

#### **Children**

KIVEXA is not recommended for treatment of children less than 12 years of age as the necessary dose adjustment cannot be made. Physicians should refer to the individual product information for lamivudine and abacavir.

#### **Elderly**

The pharmacokinetics of abacavir and lamivudine have not been studied in patients over 65 years of age. When treating elderly patients, consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, concomitant medicinal products or disease.

### **Renal impairment**

Whilst no dosage adjustment of abacavir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance. Therefore KIVEXA is not recommended for use in patients with a creatinine clearance less than 50mL/min (*see Pharmacokinetics*).

### **Hepatic impairment**

A dose reduction of abacavir is likely to be required for patients with mild hepatic impairment. As dose reduction is not possible with KIVEXA the separate preparation of abacavir should be used when this is judged necessary. KIVEXA is contraindicated in patients with moderate and severe hepatic impairment (*see Pharmacokinetics*).

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## **Contraindications**

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KIVEXA is contraindicated in patients with known hypersensitivity to abacavir or lamivudine, or to any of the excipients.

KIVEXA is contraindicated in patients with moderate and severe hepatic impairment.

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## **Warnings and Precautions**

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The special warnings and precautions relevant to both abacavir and lamivudine are included in this section. There are no additional precautions and warnings relevant to KIVEXA.

### **Hypersensitivity to abacavir** (*see also Adverse Reactions*).

In clinical studies, approximately 5% of subjects receiving abacavir developed a hypersensitivity reaction, which in rare cases has proved fatal.

- Risk Factors

Studies have shown that carriage of the HLA-B\*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. In the prospective study CNA106030 (PREDICT-1), use of pre-therapy screening for the HLA-B\*5701 allele and subsequently avoiding abacavir in patients with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66 of 847) to 3.4% (27 of 803) ( $p < 0.0001$ ) and the incidence of hypersensitivity reactions confirmed by skin patch testing from 2.7% (23 of 842) to 0.0% (0 of 802) ( $p < 0.0001$ ). Based on this study, it is estimated that 48% to 61% of patients with the HLA-B\*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0% to 4% of patients who do not have the HLA-B\*5701 allele.

Clinicians must screen for carriage of the HLA-B\*5701 allele in any HIV-infected

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

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

- **Clinical Description**

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

Some of the other symptoms of hypersensitivity may include fatigue, malaise, gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised). **The symptoms of this hypersensitivity reaction can occur at any time during treatment with abacavir**, but usually occur within the first six weeks of therapy. The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

- **Clinical Management**

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

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, KIVEXA should 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). KIVEXA, or any other medicinal product containing abacavir (ZIAGEN, TRIZIVIR), should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

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

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

If therapy with KIVEXA has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If a**

**hypersensitivity reaction cannot be ruled out, KIVEXA or any other medicinal product containing abacavir (ZIAGEN, TRIZIVIR) should not be restarted, irrespective of HLA\*B5701 carrier status.**

There have been infrequent reports of hypersensitivity reaction following reintroduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart KIVEXA in these patients, this should be done only under direct medical supervision.

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

- **Essential patient information**

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

- patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death
- patients developing signs or symptoms possibly linked with a hypersensitivity reaction **MUST CONTACT their doctor IMMEDIATELY**
- patients who are hypersensitive to abacavir should be reminded that they must never take KIVEXA or any other medicinal product containing abacavir (ZIAGEN, TRIZIVIR) again
- in order to avoid restarting KIVEXA, patients who have experienced a hypersensitivity reaction should be asked to return the remaining KIVEXA tablets to the pharmacy
- patients who have stopped KIVEXA 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 KIVEXA pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

### **Lactic acidosis/severe hepatomegaly with steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including abacavir and lamivudine. A majority of these cases have been in women.

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight

loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

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

### **Lipodystrophy**

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

Whilst all members of the protease and nucleoside reverse transcriptase inhibitor classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risk between individual members of the respective therapeutic classes.

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown.

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

### **Immune Reconstitution Syndrome**

In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii* (*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

### **Patients co-infected with hepatitis B virus**

Clinical study and marketed use of lamivudine, have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with

decompensated liver disease. If KIVEXA is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

### **Opportunistic infections**

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

### **Transmission of infection**

Patients should be advised that current antiretroviral therapy, including KIVEXA, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

### **Myocardial Infarction**

In a prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous six months was correlated with an increased risk of myocardial infarction. In a pooled analysis of GSK sponsored clinical trials no excess risk of myocardial infarction was observed with abacavir use. There is no known biological mechanism to explain a potential increase. In totality the available data from observational cohorts and from controlled clinical trials are inconclusive in regard to the relationship between abacavir treatment and the risk of myocardial infarction.

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

### ***Pregnancy***

The safe use of KIVEXA in human pregnancy has not been established. Lamivudine and abacavir have been associated with findings in animal reproductive studies (*see Non-Clinical Information*). Therefore administration of KIVEXA in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the foetus.

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

use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

### **Lactation**

Health experts recommend that where possible HIV infected women do not breast-feed their infants in order to avoid transmission of HIV. Lamivudine is excreted in human milk at similar concentrations to those found in serum. It is expected that abacavir will also be secreted into human milk, although this has not been confirmed. It is therefore recommended that mothers do not breast-feed while receiving treatment with KIVEXA.

### **Effects on ability to drive and use machines**

There have been no studies to investigate the effect of abacavir or lamivudine, on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of these medicinal products. The clinical status of the patient and the adverse event profile of KIVEXA should be borne in mind when considering the patient's ability to drive or operate machinery.

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## **Adverse Effects**

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KIVEXA contains abacavir and lamivudine, therefore the adverse events associated with these may be expected. For many of the adverse events listed it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process.

### **Hypersensitivity to abacavir** (see also Warnings and Precautions).

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

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

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

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

Skin: **rash** (usually maculopapular or urticarial)

Gastrointestinal tract: **nausea, vomiting, diarrhoea, abdominal pain,**  
mouth ulceration

Respiratory tract: **dyspnoea, cough,** sore throat, adult respiratory distress  
syndrome, respiratory failure

Miscellaneous: **fever, fatigue, malaise,** oedema, lymphadenopathy,  
hypotension, conjunctivitis, anaphylaxis

Neurological/Psychiatry: **headache,** paraesthesia

Haematological: lymphopenia

Liver/pancreas: **elevated liver function tests,** hepatic failure

Musculoskeletal: **myalgia,** rarely myolysis, arthralgia, elevated creatine  
phosphokinase

Urology: elevated creatinine, renal failure

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

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

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

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

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

The adverse events for abacavir or lamivudine are listed in the tables below by body system and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

Many of the adverse events listed occur commonly (nausea, vomiting, diarrhoea, fever, lethargy, rash) in patients with abacavir hypersensitivity. Therefore, patients with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction. If KIVEXA has been discontinued in patients due to experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only under direct medical supervision (*see Special considerations following an interruption of KIVEXA therapy in Warnings and Precautions*).

### Clinical Trial Data

Body system	Abacavir	Lamivudine
Blood and lymphatic systems disorders		Uncommon: neutropenia, anaemia, thrombocytopenia
Immune system disorders	Common: drug hypersensitivity	
Metabolism and nutrition disorders	Common: anorexia	
Nervous system disorders	Common: headache	Common: headache
Gastrointestinal disorders	Common: nausea, vomiting, diarrhoea	Common: nausea, vomiting, upper abdominal pain, diarrhoea
Hepatobiliary disorders		Uncommon: transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders		Common: rash
General disorders and administration site conditions	Common: fever, lethargy, fatigue	Common: fatigue, malaise, fever

### Postmarketing Data

In addition to the adverse events included from clinical trial data, the following adverse events listed in the table below have been identified during post-approval use of abacavir and lamivudine. These events have been chosen

for inclusion due to a potential causal connection to abacavir and/or lamivudine.

<b>Body system</b>	<b>Abacavir</b>	<b>Lamivudine</b>
Blood and lymphatic systems disorders		Very rare: pure red cell aplasia
Metabolism and nutrition disorders	Common: hyperlactataemia Rare: <sup>1</sup> Lactic acidosis	Common: hyperlactataemia Rare: <sup>1</sup> Lactic acidosis
Nervous system disorders		Very rare: paraesthesiae, peripheral neuropathy has been reported although a causal relationship to treatment is uncertain
Gastrointestinal disorders	Rare: pancreatitis, but a causal relationship to abacavir is uncertain	Rare: rises in serum amylase, pancreatitis, although a causal relationship to lamivudine is uncertain
Skin and subcutaneous tissue disorders	Common: rash (without systemic symptoms)  Very rare: erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	Common: alopecia
Musculoskeletal and connective tissue disorders		Common: arthralgia, muscle disorders  Rare: rhabdomyolysis

Redistribution/accumulation of body fat has been observed in some patients receiving combination antiretroviral therapy (see *Warnings and Precautions*). The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

<sup>1</sup>Lactic acidosis (see *Warnings and Precautions*)

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## **Interactions**

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As KIVEXA contains abacavir and lamivudine, any interactions that have been identified with these agents individually may occur with KIVEXA. Clinical studies have shown that there are no clinically significant interactions between

abacavir and lamivudine. Abacavir and lamivudine are not significantly metabolised by cytochrome P<sub>450</sub> enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P<sub>450</sub> enzymes.

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is renal.

### **Interactions relevant to abacavir**

*Ethanol* - The metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%. Given the safety profile of abacavir, these findings are not considered clinically significant. Abacavir has no effect on the metabolism of ethanol.

*Methadone* - In a pharmacokinetic study, co-administration of 600mg abacavir twice daily with methadone showed a 35% reduction in abacavir C<sub>max</sub> and a one hour delay in t<sub>max</sub>, but AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study, abacavir increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.

### **Interactions relevant to lamivudine**

*Trimethoprim* - Administration of trimethoprim/sulphamethoxazole 160mg/800mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see *Dosage and Administration*). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* (*P. carinii*) pneumonia and toxoplasmosis has not been studied.

*Zalcitabine* - Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. KIVEXA is therefore not recommended to be used in combination with zalcitabine.

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## **Overdosage**

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### **Symptoms and Signs**

No specific symptoms or signs have been identified following acute overdose with abacavir or lamivudine, apart from those listed as undesirable effects.

## **Treatment**

If overdose occurs the patient should be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

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## **Pharmaceutical Precautions**

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### ***Shelf Life***

3 years.

### ***Special precautions for storage***

Do not store above 30°C.

### ***Nature and contents of container***

KIVEXA tablets are available in opaque white, polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) blister packs each containing 30 tablets.

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## **Medicines Classification**

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Prescription Only Medicine

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## **Further Information**

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### ***Preclinical Safety Data***

There are no data available on the effects of the combination of abacavir and lamivudine in animals.

### ***Mutagenicity and carcinogenicity***

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but like many nucleoside analogues they show activity in the *in vitro* mammalian tests such as the mouse lymphoma assay. This is consistent with the known activity of other nucleoside analogues.

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

The majority of these tumours occurred at the highest abacavir dose of 330mg/kg/day in mice and 600mg/kg/day in rats. These dose levels were

equivalent to 24 to 33 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose of 110mg/kg. This is equivalent to six times the expected human systemic exposure. There is no structural counterpart for this gland in humans. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

Lamivudine has not shown any genotoxic activity in the *in vivo* studies at doses that gave plasma concentrations up to 30 to 40 times higher than clinical plasma levels. The results of long-term carcinogenicity studies in rats and mice did not show any carcinogenic potential.

### **Repeat-dose toxicity**

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

### **Reproductive toxicology**

In reproductive toxicity studies in animals, abacavir and lamivudine were shown to cross the placenta.

Abacavir demonstrated toxicity to the developing embryo and foetus only in rats at maternally toxic doses of 500mg/kg/day and above. This dose is equivalent to 33 times human therapeutic exposure based on AUC. The findings included foetal oedema, variations and malformations, resorptions, decreased foetal body weight and an increase in still births. The dose at which there were no effects on pre or post-natal development was 160mg/kg/day. This dose is equivalent to an exposure of about 10 times that in humans. Similar findings were not observed in rabbits.

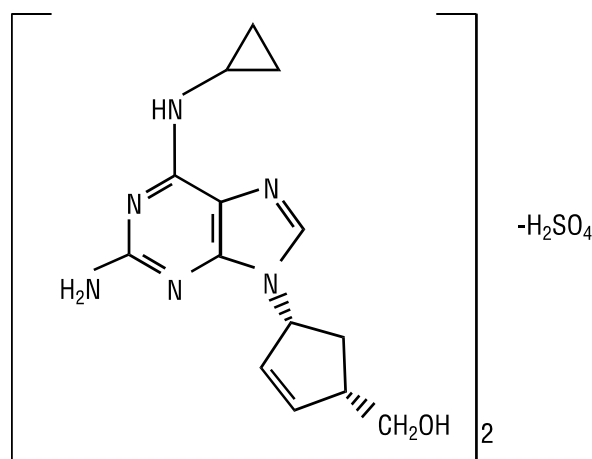
Lamivudine was not teratogenic in animal studies, but there were indications of an increase in early embryonic deaths in rabbits at exposure levels comparable to those achieved in man. However, there was no evidence of embryonic loss in rats at exposure levels of approximately 33 times the clinical exposure (based on  $C_{max}$ ).

Fertility studies in the rat have shown that abacavir and lamivudine had no effect on male or female fertility.

## **Chemical Structure**

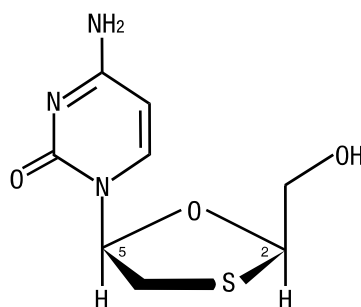
### **Abacavir sulfate**

The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the cyclopentene ring. It has a molecular formula of  $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$  and a molecular weight of 670.76 daltons. It has the following structural formula:



### Lamivudine

The chemical name of lamivudine is (2R,cis)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of  $C_8H_{11}N_3O_3S$  and a molecular weight of 229.3 daltons. It has the following structural formula:



### Clinical Studies

Abacavir and lamivudine have been used as components of antiretroviral combination therapy in naïve and experienced patients. Combination therapy has included other antiretroviral agents of the same class or different classes, such as PIs and NNRTIs. Abacavir and lamivudine from KIVEXA tablet have been shown to be bioequivalent to abacavir and lamivudine when given separately (*see Pharmacokinetics*). The clinical efficacy of antiretroviral combination therapy containing abacavir plus lamivudine, administered once or twice daily has been confirmed in the studies described below.

In a multicentre, double-blind, controlled study (CNA30024), 654 HIV-infected, antiretroviral therapy-naïve patients were randomised to receive either abacavir 300mg twice daily or zidovudine 300mg twice daily, both in combination with lamivudine 150mg twice daily and efavirenz 600mg 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 less than or equal to 50copies/mL by Week 48. Patients were stratified at baseline based on plasma HIV-1 RNA less than or equal to 100,000copies/mL or greater than 100,000copies/mL. The abacavir group was demonstrated to be non-inferior when compared to the zidovudine group in the overall and base-line viral load sub-groups. This study confirms the non-inferiority of a regimen containing abacavir plus lamivudine, compared to a more widely used regimen of zidovudine plus lamivudine.

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

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

**ITT-Exposed Population**

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

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

Genotypic analysis was attempted for all subjects with virologic failure (confirmed HIV RNA greater than 50copies/mL). There was a low overall incidence of virologic failure in both the once and twice daily treatment groups (10% and 8% respectively). Additionally, for technical reasons, genotyping was restricted to samples with plasma HIV-1 RNA greater than 500copies/mL. These factors resulted in a small sample size. Therefore no firm conclusions could be drawn regarding differences in treatment emergent mutations between the two treatment groups. Reverse transcriptase amino acid residue

184 was consistently the most frequent position for NRTI resistance-associated mutations (M184V or M184I). The second most frequent mutation was L74V. Mutations Y115F and K65R were uncommon.

### ***Excipients***

#### **Core**

Magnesium stearate, Microcrystalline cellulose, Sodium starch glycollate.

#### **Coating, Opadry Orange YS-1-13065-A containing**

Hypromellose (E464), Titanium dioxide (E171), Polyethylene glycol 400, Polysorbate 80 (E433), Sunset yellow aluminium lake (E110).

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## **Medicine Classification**

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Prescription Medicine

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## **Name and Address**

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## **Date of Preparation**

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