

PRODUCT MONOGRAPH

Pr **KIVEXA**[®]

abacavir sulfate and lamivudine tablets

Fixed-Dosed Combination

600 mg abacavir (as abacavir sulfate) and 300 mg lamivudine tablets

Antiretroviral Agent

ViiV Healthcare ULC
8455 route Transcanadienne
Montréal, Quebec
H4S 1Z1

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Pr KIVEXA®

abacavir sulfate and lamivudine tablets
Fixed-Dosed Combination

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet/ 600 mg abacavir (as abacavir sulfate) and 300 mg lamivudine	None

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

INDICATIONS AND CLINICAL USE

KIVEXA® (abacavir sulfate/lamivudine) is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults.

In one controlled study (CNA30021), more patients taking abacavir 600 mg once daily had severe hypersensitivity reactions than patients taking abacavir 300 mg twice daily. (See WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

KIVEXA® is one of multiple products containing abacavir. Before starting KIVEXA®, review medical history for prior exposure to any abacavir containing product, in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.

CONTRAINDICATIONS

KIVEXA[®] (abacavir sulfate/lamivudine) is contraindicated in

- patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- patients with known hypersensitivity to abacavir or lamivudine, or to any of the excipients.
- patients with hepatic impairment (see WARNINGS AND PRECAUTIONS).

Following a hypersensitivity reaction to abacavir, **never** restart KIVEXA[®] or any other abacavir containing product. Fatal rechallenge reactions have been associated with re-administration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Fatal Hypersensitivity Reactions**

Fatal hypersensitivity reactions have been associated with therapy with abacavir sulfate and other abacavir containing products. Therapy with KIVEXA[®] (abacavir sulfate/lamivudine) should be discontinued in patients developing signs or symptoms of hypersensitivity in 2 or more of the following groups: 1) fever, 2) rash, 3) gastrointestinal (including nausea, vomiting, diarrhea or abdominal pain), 4) constitutional (including generalized malaise, fatigue or achiness), 5) respiratory (including pharyngitis, dyspnea, cough and abnormal chest x-ray findings, predominantly infiltrates, which can be localized) (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions to Abacavir). To minimize 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 (acute onset of respiratory diseases, gastroenteritis or reactions to other medications).

The symptoms of a hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks of therapy. **KIVEXA[®] or any other medicinal product containing abacavir (e.g. 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.** Severe or fatal hypersensitivity reactions can occur within hours after KIVEXA[®] re-introduction in patients who have no identified history or undiagnosed symptoms of hypersensitivity during their initial period of use of KIVEXA[®].

Patients who carry the HLA-B*5701 allele are at a significant increased risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, it is recommended that screening for HLA-B*5701 status be undertaken. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended.

Cases of abacavir hypersensitivity have occurred in patients who are HLA-B*5701 negative. The clinical diagnosis of suspected hypersensitivity to abacavir remains the basis for clinical decision making in all patients. Therefore, it is important to permanently discontinue abacavir and not rechallenge with abacavir if hypersensitivity cannot be ruled out, regardless of the presence or absence of the HLA-B*5701 allele due to the potential for a severe or even fatal reaction (see WARNINGS and PRECAUTIONS: Hypersensitivity Reaction: Risk Factors: HLA-B*5701 Allele).

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including KIVEXA[®] and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with KIVEXA[®] should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations) (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

- **Post-Treatment Exacerbation of Hepatitis**

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. KIVEXA[®] is not indicated for the treatment of chronic HBV infection and the safety and efficacy of KIVEXA[®] have not been established in patients coinfecting with HBV and HIV. Exacerbations of hepatitis B have been reported in patients after the discontinuation of antiretroviral therapy. Patients coinfecting with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with KIVEXA[®] (see ADVERSE EVENTS, Post-Market Adverse Drug Reactions).

- **Pancreatitis**

Pancreatitis has been observed in some patients receiving abacavir and lamivudine. However it is not clear whether these cases were due to drug treatment or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of KIVEXA[®] until diagnosis of pancreatitis is excluded (see ADVERSE EVENTS, Post-Market Adverse Drug Reactions).

- **Pancreatitis in Pediatric Patients**

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine containing products should be used with caution. Treatment with lamivudine containing products should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

General

KIVEXA[®] (abacavir sulfate/lamivudine) is a fixed-dose combination of abacavir sulfate and lamivudine. KIVEXA[®] should not be administered concomitantly with either abacavir or lamivudine.

Hypersensitivity Reactions to Abacavir

Serious and sometimes fatal hypersensitivity reactions have been associated with therapy with abacavir sulfate, one of the two active ingredients of KIVEXA[®]. Patients who carry the HLA-B*5701 allele are at a significantly increased risk for experiencing a hypersensitivity reaction to abacavir. Other less common signs or symptoms of hypersensitivity include fever, skin rash, fatigue, myolysis, edema, paresthesia, anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions, gastrointestinal symptoms such as nausea, vomiting, diarrhea or abdominal pain, and respiratory signs and symptoms such as pharyngitis, dyspnea, cough and abnormal chest x-ray findings predominantly infiltrates, which can be localized.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

The diagnosis of a hypersensitivity reaction should be carefully considered for patients presenting with symptoms of acute onset respiratory diseases, even if alternative respiratory diagnoses (pneumonia, bronchitis, pharyngitis or flu-like illness) are possible. 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 minimize 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 re-started even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

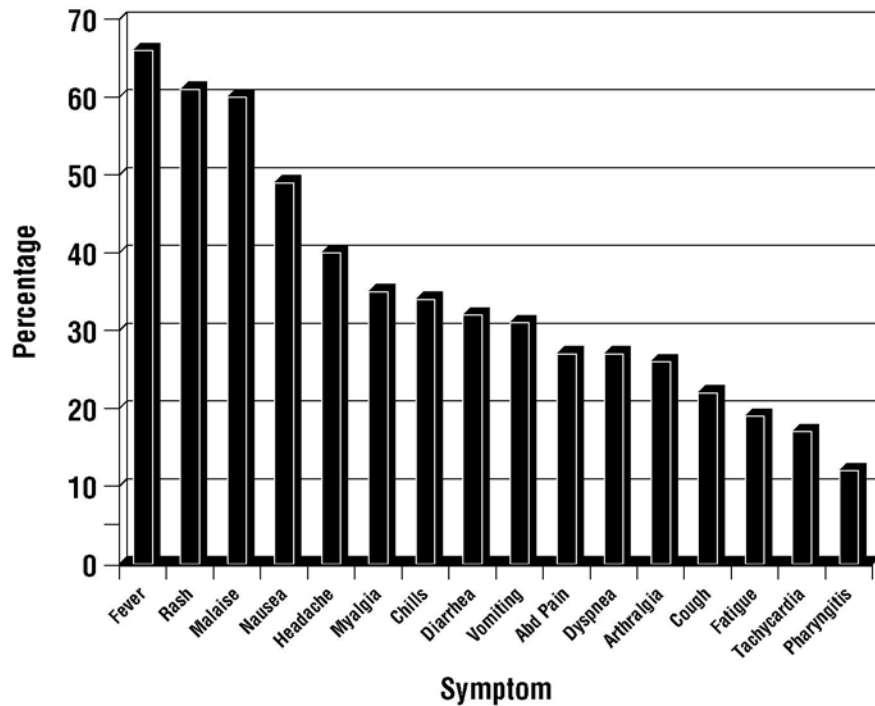
Severe or fatal hypersensitivity reactions can occur within hours after KIVEXA[®] re-introduction in patients who have no identified history or unrecognized symptoms of hypersensitivity during their initial period of use of KIVEXA[®].

Regardless of a patient's HLA-B*5701 status, if therapy with KIVEXA[®] or any other medicinal product containing abacavir (ZIAGEN[®], TRIZIVIR[®]) 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 (e.g. ZIAGEN[®], TRIVIZIR[®]) should not be restarted.**

If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of KIVEXA[®] or any other abacavir containing product and that reintroduction of KIVEXA[®] or introduction of any other abacavir containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

Overall, in clinical trials conducted before the introduction of screening for the HLA-B*5701 allele, hypersensitivity reactions have been reported in approximately 8% of 2,670 patients (n=206) in 9 clinical trials (range: 2 to 9%) with enrolment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity in the nine studies were collected on a detailed data collection module. This reaction is characterized by the appearance of symptoms indicating multi-organ / body-system involvement. Symptoms can occur at any time during therapy, however they usually appear within the first 6 weeks (median time to onset is 11 days) of initiation of treatment with abacavir (see ADVERSE REACTIONS).

Figure 1 Hypersensitivity Related Symptoms Reported with Greater Than or Equal to 10 Percent Frequency in Clinical Trials (n = 206 Patients)



In a controlled study (CNA30021), more patients taking abacavir 600 mg once daily had severe hypersensitivity reactions than patients taking abacavir 300 mg twice daily (see DOSAGE AND ADMINISTRATION). In this study, 4 patients (11%) receiving abacavir 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving abacavir 300 mg twice daily.

A warning card with information for the patient about this hypersensitivity reaction is included in the KIVEXA[®] pack (see INFORMATION FOR THE CONSUMER: Warning Card).

Risk Factors: HLA-B*5701 Allele:

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. CNA106030 (PREDICT-1), a randomized, double blind study, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naïve HIV-1 infected adults (n = 1,650). In this study, use of pre-therapy screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803) ($p < 0.0001$). Based on this study, it is estimated that 61% of patients with the HLA-B*5701 allele will develop a clinically suspected hypersensitivity reaction during the course of abacavir treatment compared with 4% of patients who do not have the HLA-B*5701 allele.

Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment with abacavir. Screening is also recommended prior to re-initiating abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, initiating or re-initiating treatment with an abacavir containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances where potential benefit outweighs the risk.

Skin patch testing is used as a research tool and should not be used to aid in the clinical diagnosis of abacavir hypersensitivity.

In any patient treated with abacavir, the clinical diagnosis of a 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.

Carcinogenesis and Mutagenesis

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. At systemic exposures approximately nine times higher than those in humans at the therapeutic dose, abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation (see TOXICOLOGY: Mutagenicity).

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 subcutis of female rats.

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. These dose levels were equivalent to 24 to 33 times the expected systemic exposure in humans (see TOXICOLOGY: Carcinogenicity).

Cardiovascular

The results of a prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy (N=33,347) suggest that current or recent use (within the past 6 months) of abacavir may be associated with a potential increased risk of myocardial infarction. This elevated risk does not appear to increase further over time, and no excess risk was present in patients who had stopped taking abacavir more than 6 months previously. The relative risk of myocardial infarction was estimated to be 1.9 (95% CI 1.47-2.45). The absolute myocardial infarction rate was 6.1/1000 patient years of exposure for those recently exposed to abacavir compared to an absolute myocardial infarction rate of 2.6/1000 patient years of exposure for those not recently exposed. In addition, the absolute myocardial infarction rate ranged from 3.4 to 3.7/1000 patient years of exposure for patients recently exposed to other NRTIs (i.e. zidovudine, stavudine and lamivudine).

In a pooled analysis of GSK sponsored clinical trials (N=9639), no increased risk of myocardial infarction was observed with abacavir use. At this time, though the available data do not allow a definitive conclusion regarding the association between the use of abacavir and an increased risk of myocardial infarction, it is recommended that physicians discuss the potential benefits and risks of abacavir with their patients.

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, hyperlipidemia, diabetes mellitus and smoking).

Endocrine and Metabolism

Fat Redistribution

Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (“buffalo hump”), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy.

The mechanism and long term consequences of these events are currently unknown. A causal relationship has not been established.

Hematologic

Very rare occurrences of pure red cell aplasia have been reported with lamivudine use. Discontinuation of lamivudine has resulted in normalization of hematologic parameters in patients with suspected lamivudine induced pure red cell aplasia.

Hepatic/Biliary/Pancreatic

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 alone or in combination, including abacavir and lamivudine, in the treatment of HIV infection. A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalized weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnea and tachypnea).

Obesity and prolonged nucleoside exposure may be risk factors. Particular 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.

Use With Interferon and Ribavirin Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of KIVEXA[®]. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g. loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV/HCV coinfecting patients (see Drug Interactions), hepatic decompensation (some fatal) has occurred in HIV/HCV coinfecting patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and KIVEXA[®] should be closely monitored for treatment associated toxicities, especially hepatic decompensation. Discontinuation of KIVEXA[®] should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation.

Patients with impaired hepatic function

Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because KIVEXA[®] is a fixed dose combination and cannot be dose adjusted, KIVEXA[®] is contraindicated for patients with hepatic impairment.

Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) who had confirmed cirrhosis.

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 therefore required in patients with mild hepatic impairment. The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment.

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

Patients coinfecting 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 abacavir/lamivudine is discontinued in patients coinfecting with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Immune

Immune reconstitution syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP and TB), which may necessitate further evaluation and treatment.

Renal

Patients with Impaired Renal Function

Lamivudine requires dose adjustment in the presence of renal insufficiency. Because KIVEXA[®] is a fixed dose combination and cannot be dose adjusted, it is not recommended for use in patients with creatine clearance < 50 mL/min.

Respiratory

Severe respiratory symptoms, some indicative of adult respiratory distress syndrome (ARDS), occur in a small proportion of hypersensitivity reaction cases. ARDS or respiratory failure appears more likely to occur in a rechallenge situation.

Special Populations

Pregnant Women

The safe use of abacavir sulfate/lamivudine in human pregnancy has not been established. Lamivudine and abacavir have been associated with findings in animal reproductive studies (see TOXICOLOGY). Therefore, administration of KIVEXA[®] in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the fetus.

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.

To monitor maternal-fetal outcomes of pregnant women exposed to KIVEXA[®], an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling ViiV Healthcare ULC's Drug Safety Department (1-877-393-8448).

Nursing Women

It is recommended that HIV infected women do not breastfeed their infants, under any circumstances, 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 breastfeed while receiving treatment with KIVEXA[®].

Pediatrics (< 18 years of age)

The safety and effectiveness of KIVEXA[®] has not been studied in patients < 18 years of age. Physicians should refer to the individual product information for lamivudine and abacavir.

Geriatrics (> 65 years of age)

KIVEXA[®] should not be used in patients over 65 years of age. Physicians should refer to the individual product information for lamivudine and abacavir (see Use of KIVEXA[®] in Patients with CoMorbid Conditions and in the Elderly).

Use of KIVEXA[®] in Patients with CoMorbid Conditions and in the Elderly

KIVEXA[®] should not be used in patients over 65 years of age, or in patients with comorbid conditions such as hepatic or renal failure, as this dosing regimen has not been studied in this population. The use of KIVEXA[®] has not been studied in elderly patients or patients with comorbid conditions.

Therapy Experienced Patients

In clinical trials, patients with prolonged prior nucleoside reverse transcriptase inhibitor (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy experienced patients (see MICROBIOLOGY: Cross Resistance).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

KIVEXA[®] (abacavir sulfate/lamivudine) 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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Hypersensitivity to Abacavir

Overall, in clinical trials conducted before the introduction of screening for the HLA-B*5701 allele, hypersensitivity to abacavir was reported in 8% of patients in 9 clinical trials (range: 2 to 9%). This reaction is characterized by the appearance of symptoms indicating multi-organ / body system involvement.

Product containing abacavir **must not** be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life threatening hypotension and death. Patients developing signs or symptoms of hypersensitivity should discontinue treatment as soon as a hypersensitivity reaction is first suspected, and must seek medical evaluation immediately. To avoid a delay in diagnosis and minimize 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 (e.g. respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). KIVEXA[®], or any other medicinal product containing abacavir, should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

Severe or fatal hypersensitivity reactions can occur within hours after KIVEXA[®] re-introduction in patients who have no identified history or unrecognized symptoms of hypersensitivity during their initial period of use of KIVEXA[®] (see WARNINGS AND PRECAUTIONS).

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.

Gastrointestinal tract:	abdominal pain, diarrhea , mouth ulceration, nausea, vomiting
Hematological:	lymphopenia
Liver/pancreas:	elevated liver function tests , hepatic failure
Miscellaneous:	anaphylaxis, conjunctivitis, edema, fatigue, fever , hypotension, lymphadenopathy, malaise
Musculoskeletal:	arthralgia, elevated creatine phosphokinase, myalgia , rarely myolysis,
Neurological/Psychiatry:	headache , paresthesia
Respiratory tract:	adult respiratory distress syndrome, cough, dyspnea , respiratory failure, sore throat
Skin:	rash (usually maculopapular or urticarial)
Urology:	elevated creatinine, renal failure

Some patients with hypersensitivity were initially thought to have respiratory disease (e.g. pneumonia, bronchitis, or pharyngitis), a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity 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 a hypersensitivity reaction cannot be ruled out, KIVEXA[®], or any other medicinal product containing abacavir (e.g. 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. Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue KIVEXA[®] and must never be rechallenged with KIVEXA[®], or any other medicinal product containing abacavir (e.g. ZIAGEN[®], TRIZIVIR[®]).

There have been infrequent reports of hypersensitivity reactions following re-introduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (i.e. 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 Table 1 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), and very rare (< 1/10,000).

Many of the adverse events listed occur commonly (i.e. nausea, vomiting, diarrhea, fever, lethargy and 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 their experiencing any one of these symptoms and a decision is made to restart abacavir, this must be done only under direct medical supervision (see WARNINGS AND PRECAUTIONS).

Table 1 Adverse Events Observed During Clinical Trials

Body System	Abacavir	Lamivudine
Blood and lymphatic systems disorders		Uncommon: neutropenia, anemia, thrombocytopenia
Immune system disorders	Common: drug hypersensitivity	
Metabolism and nutrition disorders	Common: anorexia, hyperlactatemia Rare: lactic acidosis (see WARNINGS AND PRECAUTIONS)	
Nervous system disorders	Common: headache	Common: headache
Gastrointestinal disorders	Common: nausea, vomiting, diarrhea Rare: pancreatitis has been reported, but a causal relationship to abacavir treatment is uncertain	Common: nausea, vomiting, upper abdominal pain, diarrhea
Hepatobiliary disorders		Uncommon: transient rises in liver enzymes (AST, ALT)
Skin and subcutaneous tissue disorders	Common: rash (without systemic symptoms) Very rare: erythema multiforme, SJS and TEN	Common: rash
General disorders and administration site conditions	Common: fever, lethargy, fatigue	Common: fatigue, malaise, fever

In study CNA30021, treatment emergent clinical adverse reactions (rated by the investigator as at least moderate) with a $\geq 5\%$ frequency during therapy with abacavir 600 mg once-daily and efavirenz 600 mg once daily were similar. For hypersensitivity reactions, patients receiving abacavir once daily showed a rate of 9% in comparison to a rate of 7% for patients receiving abacavir twice daily. However, patients receiving abacavir 600 mg once daily experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared to patients who received abacavir 300 mg twice daily. Five percent (5%) of patients receiving abacavir 600 mg once daily had severe drug hypersensitivity reactions compared to 2% of patients receiving abacavir 300 mg twice daily. Two percent (2%) of patients receiving abacavir 600 mg once daily had severe diarrhea while none of the patients receiving abacavir 300 mg twice daily had this event.

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside experienced pediatric patients receiving 3TC[®] alone or in combination with other antiretroviral agents. In an open label, dose escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with 3TC[®]. Three of these patients died of complications of pancreatitis. In a second open label study (NUCA2005), 12 patients (18%) developed pancreatitis. In study ACTG300, pancreatitis was not observed in 236 patients randomized to 3TC[®] plus RETROVIR[®] (AZT[™]). Pancreatitis was observed in one patient in this study who received open label 3TC[®] in combination with RETROVIR[®] (AZT[™]) and ritonavir following discontinuation of didanosine monotherapy.

Post-Market Adverse Drug Reactions

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

These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to abacavir and lamivudine, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Body as a whole: anaphylaxis, redistribution/accumulation of body fat, weakness

Digestive: stomatitis

Endocrine/Metabolic: hepatic steatosis, hyperglycemia, hyperlactatemia, lactic acidosis

Hematological: pure red cell aplasia

Hemic and Lymphatic: anemia, lymphadenopathy, splenomegaly

Hepatic: hepatic steatosis, lactic acidosis

Musculoskeletal: muscle disorders including rarely rhabdomyolysis, arthralgia

Nervous: paresthesia, peripheral neuropathy

Other: alopecia

Skin: pruritus, rash, urticaria. Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir, primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of the clinical signs and symptoms between hypersensitivity to abacavir, SJS and TEN and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases. There have been reports of erythema multiforme with abacavir use.

DRUG INTERACTIONS

Overview

As KIVEXA[®] (abacavir sulfate/lamivudine) 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 metabolized by cytochrome P₄₅₀ 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 metabolized by major P₄₅₀ 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.

Drug-Drug Interactions

The drugs listed in the following tables are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 2 Interactions Relevant to Abacavir

Proper name	Effect	Clinical comment
Ethanol	In men, the metabolism of abacavir sulfate is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%.	The clinical significance of this is unknown. In men, abacavir sulfate has no effect on the metabolism of ethanol. This interaction has not been studied in women.
Methadone	In a pharmacokinetic study, coadministration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir C_{max} and a one hour delay in t_{max} , but 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 retitration may be required.
Retinoids		Retinoid compounds, such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.
Ribavirin	<i>In vitro</i> data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine.	No pharmacokinetic (e.g. plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g. loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi drug regimen to HIV/HCV coinfecting patients (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).

Table 3 Interactions relevant to lamivudine

Proper name	Effect	Clinical comment
Trimethoprim	Administration of trimethoprim/ sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component.	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 coadministration of lamivudine with higher doses of co-trimoxazole used for the treatment of <i>Pneumocystis carinii</i> 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 not recommended to be used in combination with zalcitabine.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

A patient information leaflet and warning card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

KIVEXA[®] (abacavir sulfate/lamivudine) can be taken with or without food.

Recommended Dose and Dosage Adjustment

Because KIVEXA[®] is a fixed dose tablet it should not be prescribed for patients requiring dosage adjustments, such as those who weigh less than 40 kg, those with creatinine clearance < 50 mL/min, those with hepatic impairment or those experiencing dose limiting adverse events. 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.

Adults (≥ 18 years)

The recommended dose of KIVEXA[®] is one tablet once daily.

The use of abacavir 600 mg once daily may be associated with a higher incidence of severe hypersensitivity reactions.

Children

Physicians should refer to the individual product information for lamivudine and abacavir. The safety and effectiveness of KIVEXA[®] have not been studied in patients less than 18 years of age (see WARNINGS AND PRECAUTIONS).

Elderly

The use of KIVEXA[®] has not been studied in elderly patients or patients with comorbid conditions (see WARNINGS AND PRECAUTIONS).

Missed Dose

It is important to take KIVEXA[®] as prescribed to ensure the patient gets maximum benefit. If the patient forgets to take a dose, they should take it as soon as they remember, and then continue as before. Patients must not take more than one tablet to make up for forgotten individual doses.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

There is no known antidote for KIVEXA[®] (abacavir sulfate/ lamivudine). If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required. Although no data are available, administration of activated charcoal may be used to aid in the removal of unabsorbed drug. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis. Because a negligible amount of lamivudine was removed via (4 hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered.

Single doses up to 1,200 mg and daily doses up to 1,800 mg of abacavir sulfate have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. No specific signs or symptoms have been identified following such overdose.

One case of acute overdose in an adult ingesting 6 g of 3TC[®] was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. One other adult patient, in error, ingested lamivudine 1,200 mg per day plus zidovudine 1,200 mg per day for approximately 2 weeks; he had a Grade 3 decrease in absolute neutrophil count that resolved upon reduction of doses of lamivudine and zidovudine. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of 3TC[®]; the second case involved the use of 5 mg/kg of 3TC[®] twice daily for 30 days. There were no clinical signs or symptoms noted in either case.

In Phase I studies, lamivudine was administered at doses up to 20 mg/kg per day (i.e. approximately five times the usual recommended dose in adults) without serious consequences.

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

KIVEXA[®] (abacavir sulfate/lamivudine) is a fixed dose combination of two nucleoside analogues (abacavir and lamivudine). Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs), and are potent, selective inhibitors of HIV-1 and HIV-2. Both abacavir and lamivudine are metabolized 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). Inhibition of RT is via viral DNA chain termination after nucleoside analogue. Carbovir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

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 h sampling period, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 h, compared to the geometric mean abacavir plasma half-life in this study of 2.6 h.

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

For patients receiving lamivudine 300 mg once daily, the terminal intracellular half-life of lamivudine-TP was prolonged to 16 to 19 h, compared to the plasma lamivudine half-life of 5 to 7 h.

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 300 mg and abacavir 600 mg 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 (see CLINICAL TRIALS).

STORAGE AND STABILITY

Stability and Storage Recommendations

Store KIVEXA[®] (abacavir sulfate/lamivudine) tablets between 15 to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

KIVEXA[®] (abacavir sulfate/lamivudine) tablets are orange, film coated, modified, capsule shaped tablets, debossed with GS FC2 on one side and the other side plain containing 600 mg abacavir as abacavir sulfate and 300 mg lamivudine. Available in blisters of 30 tablets.

Composition

Each KIVEXA[®] tablet contains 600 mg of abacavir as abacavir sulfate and 300 mg lamivudine. In addition, each tablet contains the following non-medicinal ingredients: hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, sodium starch glycolate, titanium dioxide and FD & C Yellow #6 Aluminum Lake.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

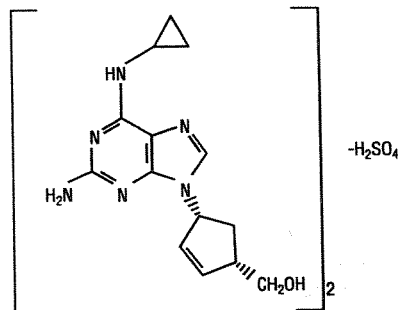
Drug Substance

Proper name: abacavir sulfate

Chemical name: (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)

Molecular formula and molecular mass: (C₁₄H₁₈N₆O)₂·H₂SO₄, 670.76

Structural formula:



Physicochemical properties:

Description: abacavir sulfate is a white to off-white powder with a melting point around 219°C followed by decomposition.

Solubility: The aqueous solubility and pH of abacavir sulfate was determined at 25°C as follows:

Solvent	Solubility (mg/mL)	pH
Distilled water	77	3.1
0.1 M HCl	110	1.6
0.1 M NaOH	22	12.2

pK_a: The pK_a for abacavir have been determined by UV spectroscopy at 25°C as follows: pK₁ = 0.4, pK₂ = 5.06.

PHARMACEUTICAL INFORMATION

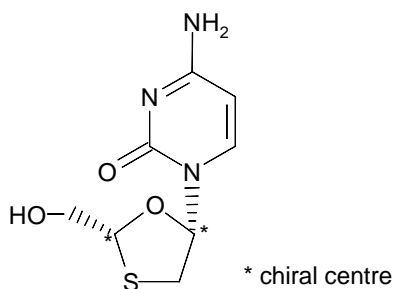
Drug Substance

Proper name: lamivudine

Chemical name: 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-(2R-cis)-

Molecular formula and molecular mass: $C_8H_{11}N_3O_3S$ 229.3

Structural formula:



Physicochemical properties:

Description: Lamivudine is a white to off-white crystalline solid with a melting point of 176°C.

Solubility:

Solvent	Temperature (°C)	Solubility (mg/mL)
Water	15	61.3
Water	25	98.1
Methanol	25	33.4
Ethanol	25	11.4
Acetone	25	0.94

pKa and pH: The pH value of a 1% w/v solution in water is approximately 6.9.
The pK_a determined by UV is 4.30.

CLINICAL TRIALS

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[®] (abacavir sulfate/lamivudine) tablets have been shown to be bioequivalent to abacavir and lamivudine when given separately (see DETAILED PHARMACOLOGY, Pharmacokinetics). The clinical efficacy of antiretroviral combination therapy containing abacavir plus lamivudine, administered once or twice daily, has been confirmed in the study below.

A once daily regimen of abacavir and lamivudine was investigated in a multi centre, double blind, controlled study (CNA30021) of 770 HIV infected, therapy naïve adults. They were randomized to receive either abacavir 600 mg once daily or 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. Patients were stratified at baseline based on plasma HIV-1 RNA \leq 100,000 copies/mL or $>$ 100,000 copies/mL. The duration of double blind treatment was at least 48 weeks. The results are summarized in Table 4.

Table 4 Virological Response Based on Plasma HIV-1 RNA Less Than 50 copies/mL at Week 48 ITT – Exposed Population (Protocol CNA30021)

Populations	abacavir once/day + lamivudine + EFV (N = 384)	abacavir twice/day + lamivudine + EFV (N= 386)
Sub-group by baseline RNA		
\leq 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 baseline viral load subgroups.

DETAILED PHARMACOLOGY

Pharmacokinetics

KIVEXA[®] (abacavir sulfate/lamivudine) tablets have been shown to be bioequivalent to abacavir and lamivudine administered separately. This was demonstrated in a single dose, three way crossover bioequivalence study of KIVEXA[®] (fasted) versus 2 x 300 mg abacavir tablets plus 2 x 150 mg lamivudine tablets (fasted) versus KIVEXA[®] administered with a high fat meal, in healthy volunteers (n = 25).

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.

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 80-85% respectively. The mean time to maximal serum concentrations (t_{\max}) is about 1.5 and 1.0 hours for abacavir and lamivudine respectively. Following a single oral dose of 600 mg of abacavir, the mean C_{\max} is 4.26 $\mu\text{g/mL}$ and the mean AUC_{∞} is 11.95 $\mu\text{g}\cdot\text{h/mL}$. Following multiple dose oral administration of lamivudine 300 mg once daily for seven days the mean steady state C_{\max} is 2.04 $\mu\text{g/mL}$ and the mean AUC_{24} is 8.87 $\mu\text{g}\cdot\text{h/mL}$.

Distribution: Intravenous studies with abacavir and lamivudine showed that the mean apparent volume of distribution is 0.8 and 1.3 L/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 (< 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 0.08 $\mu\text{g/mL}$ or 0.26 μM when abacavir is given at 600 mg twice daily. The mean ratio of CSF/serum lamivudine concentrations 2-4 hours 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 metabolized by the liver with less than 2% of the administered dose being renally excreted as unchanged compound. The primary pathways of metabolism in humans 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 (< 10%).

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 feces.

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

Special Patient Populations

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

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 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 metabolized 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 < 50 mL/min; therefore the separate preparation of lamivudine (3TC[®]) should be used to treat these patients.

MICROBIOLOGY

Abacavir and lamivudine are potent, selective inhibitors of HIV-1 and HIV-2 replication *in vitro*. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Intracellularly, abacavir and lamivudine are phosphorylated to their active 5'-triphosphate metabolites, carbovir-triphosphate (CBV-TP) and lamivudine and triphosphate (L-TP). *In vitro* L-TP has an intracellular half life of approximately 10.5 to 15.5 hours. The principal mode of action of L-TP is inhibition of HIV reverse transcription (RT) via viral DNA chain termination. L-TP is a weak inhibitor of mammalian α , β and γ -DNA polymerases. The relationship between *in vitro* susceptibility of HIV and the inhibition of HIV replication in humans has not been established.

In Vitro Activity

Abacavir:

The *in vitro* anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1 IIB in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1 BaL in primary monocytes/macrophages and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μ M against HIV-1 IIB, and was $0.26 \pm 0.18 \mu$ M (1μ M = 0.28 μ g/mL) against eight clinical isolates. The IC_{50} of abacavir against HIV-1 BaL varied from 0.07 to 1.0 μ M. 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.

Lamivudine:

The antiviral activity of lamivudine has been studied in combination with other antiretroviral compounds (zidovudine, zalcitabine and didanosine) using HIV-1 infected MT-4 cells as the test system. The MTT formazan assay demonstrated synergistic antiretroviral activity between lamivudine and zidovudine, additive antiretroviral activity between lamivudine and zalcitabine and additive antiretroviral activity between lamivudine and didanosine. The combination of lamivudine/zidovudine also showed synergistic activity in a variable ratio study.

Drug Resistance

Abacavir:

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 IC₅₀ over wild type virus, which may be a clinically relevant level. The mutations selected by *in vitro* passage have also been observed among isolates obtained from patients participating in clinical trials, with L74V and M184V being the most common. Combination therapy with ZIAGEN[®] (abacavir sulfate) and zidovudine delays the emergence of mutations associated with resistance to ZIAGEN[®] compared with monotherapy with ZIAGEN[®].

Lamivudine:

In nonclinical studies, lamivudine resistant isolates of HIV have been selected *in vitro*. A known mechanism of lamivudine resistance is the change in the 184 amino acid of RT from methionine to either isoleucine or valine. *In vitro* studies indicate that zidovudine resistant viral isolates can become sensitive to zidovudine when they acquire the 184 mutation. The clinical relevance of such findings remains, however, not well defined.

For isolates collected in clinical studies, phenotypic resistance data showed that resistance to lamivudine monotherapy developed within 12 weeks. Evidence in isolates from antiretroviral-naïve patients suggests that the combination of lamivudine and zidovudine delays the emergence of mutations conferring resistance to zidovudine. Combination therapy with lamivudine plus zidovudine did not prevent phenotypic resistance to lamivudine. However, phenotypic resistance to lamivudine did not limit the antiretroviral activity of combination therapy with lamivudine plus zidovudine. In antiretroviral therapy-naïve patients, phenotypic resistance to lamivudine emerged more slowly on combination therapy than on lamivudine monotherapy. In the zidovudine experienced patients on lamivudine plus zidovudine, no consistent pattern of changes in phenotypic resistance to lamivudine or zidovudine was observed.

Cross-resistance

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

In vitro isolates resistant to abacavir might also show reduced sensitivity to lamivudine, zalcitabine, tenofovir, emtricitabine and/or didanosine, but remain sensitive to zidovudine and stavudine.

Observed During Clinical Trial:

A once daily regimen of abacavir and lamivudine was investigated in a multi centre, double blind, controlled study (CNA30021) of 770 HIV-infected, therapy naïve adults. They were randomized to receive either abacavir 600 mg once daily or 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. Patients were stratified at baseline based on plasma HIV-1 RNA \leq 100,000 copies/mL or $>$ 100,000 copies/mL. The duration of double blind treatment was at least 48 weeks.

Genotypic analysis was attempted for all subjects with virologic failure (confirmed HIV RNA $>$ 50 copies/mL). There was a low overall incidence of virologic failure in both the once and twice daily treatment groups (10 and 8% respectively). Additionally, for technical reasons, genotyping was restricted to samples with plasma HIV-1 RNA $>$ 500 copies/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.

Cytotoxicity

The results of cytotoxicity studies in various assays have shown little cytotoxic action with lamivudine. Cytotoxicity of lamivudine was compared with that of zidovudine, zalcitabine, and didanosine in four T-lymphoblastoid cell lines; one monocyte/macrophage-like cell line; one B-lymphoblastoid cell line; and peripheral blood lymphocytes (PBLs) using both cell proliferation (CP) and [³H]-thymidine uptake (Td) assays. In the CP assay, lamivudine was the least toxic of the four compounds. [³H]-thymidine uptake results demonstrated a similar trend to those from the CP assays. Lamivudine had no cytotoxic effect when incubated for 10 days with phytohemagglutinin (PHA)-activated human lymphocytes or human macrophages.

The cytotoxicity of combinations of lamivudine with zidovudine, zalcitabine, or didanosine was evaluated in PHA-activated PBLs and CEM cells by measuring cellular uptake of [³H]-thymidine. Lamivudine greatly reduced the cytotoxicity of zalcitabine, slightly reduced the cytotoxicity of zidovudine in some cases, and did not alter the cytotoxicity of didanosine.

In myelotoxicity studies *in vitro*, lamivudine demonstrated no toxic effects against erythroid, granulocyte-macrophage, pluripotent, or stromal progenitor cells from healthy human donors. Lamivudine was not toxic to human hematopoietic supportive stroma, nonadherent hematopoietic cells, or stromal fibroblasts and produced minimal changes in cytokine (GM-CSF) production from mitogen stimulated bone marrow stromal cells. Lamivudine was less toxic than zidovudine, zalcitabine, ara-C, 3FT, and stavudine in these studies. In another study, lamivudine was not toxic to activated human T-cells.

TOXICOLOGY

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

Acute Toxicity

Acute toxicity studies with abacavir and lamivudine have been performed in the mouse and rat.

Abacavir:

Single oral or intravenous dose acute toxicity studies in the mouse and rat revealed no significant effects. The maximum non-lethal oral dose of abacavir in the mouse and rat was at least 100 and 115 fold greater, respectively, than the maximum intended therapeutic dose in humans of 300 mg b.i.d. (12 mg(base)/kg/day for a 50 kg person). The results are summarized in Table 5.

Table 5 Median Lethal Doses of Abacavir in Mice and Rats Following Oral and Intravenous Administration

Species (strain)	Route of Administration	Sex	Median Lethal Dose (mg/kg)		Multiple of Therapeutic Dose*
			Succinate	Base	
Mouse (CD-1)	Oral	Male	1,731.68	1,226	102
		Female	>1,900	1,345	112
	Intravenous	Male	>260	>184	>15
		Female	>260	>184	>15
Rat (CD)	Oral	Male	>2,000	>1,416	118
		Female	>2,000	>1,416	118
	Intravenous	Male	>260	>184	>15
		Female	>260	>184	>15

Key:

* = Median lethal dose/therapeutic dose (300 mg (base)b.i.d., equivalent to 12 mg(base)/kg/day based on a 50 kg person).

Lamivudine:

The acute oral administration of very high doses of lamivudine (two doses of 2,000 mg/kg) in mice was associated with transient increases in sexual activity in males and general activity in males and females. There were no deaths and no evidence of target organ toxicity. Therefore the maximum non-lethal oral dose of lamivudine in mice is greater than two doses of 2,000 mg/kg.

The acute intravenous administration of lamivudine at 2,000 mg/kg was well tolerated by both mice and rats and was not associated with any target organ toxicity. A number of non-specific clinical signs were observed which were more severe in rats but were all of relatively short duration.

Long-term toxicity

Abacavir:

Repeated oral administration of abacavir succinate to mice at 330 mg/kg/day for up to 6 months, and to monkeys at 300 mg/kg/day for up to 52 weeks, or abacavir sulfate to rats at 530 mg/kg/day for up to 3 months, resulted in few changes which were mostly reversible.

The only consistent findings in rodents and monkeys were changes in the liver. Increases in liver weights seemed to be dose related in the monkey. Microscopically, slight centrilobular hepatocellular hypertrophy was seen in these animal species. Occasional individual cell necrosis, pigment deposits in centrilobular hepatocyte and Kupffer cells were seen in mice and rats. In high dose monkeys, slightly swollen mitochondria, a decrease in the amount of rough endoplasmic reticulum and an increase in the number of lysosomes were observed using electron microscopy.

The results are summarized in Table 6.

Table 6 Findings in Mice, Rats and Monkeys Following Long Term Oral Administration of Abacavir

Species (Strain) Report No. [Salt used]	Study Duration	Number of Animals/Group		Dosage (mg/kg/day)		Toxic Effects Observed
		Males	Females	Salt	Base	
Mouse (CD1) RD1996/00245/00 [Abacavir succinate]	6 months	30 30 40	30 30 40	55 110 330	39 78 234	Very slight increase in serum cholesterol in males at 110 mg and both sexes at 330 mg. Increased liver weight and hepatocellular hypertrophy seen at 330 mg. Dose related and reversible increases in endogenous pigment deposition in Kupffer cells and centrilobular hepatocytes. Very slight increase in cecal crypt epithelial cell apoptosis associated with submucosal inflammation at 330 mg.
Rat (Han Wistar) RD1997/03595/00 [Abacavir hemisulfate]	3 months	5 5 5	5 5 5	35 135 530	25 96 375	Slight decreases in serum albumin and total protein and a slight increase in serum cholesterol at 530 mg. Very slight decrease in serum albumin in females at 135 mg. Slight increase in liver weight, centrilobular hepatocellular hypertrophy and accumulation of brown pigment in Kupffer cells at 530 mg. Similar liver changes also observed in males at 135 mg. Trace hypertrophy of thyroid follicular epithelium and germ cell loss in testes at 530 mg.
Monkey (Cynomolgus) RD1996/00310/01 [Abacavir succinate]	12 months	7 7 9	7 7 9	50 140 300†	35 99 212	Emesis at 420 mg decreased when dosage reduced to 300 mg. Hunched posture, hypoactivity, decreased appetite and/or abnormal or reduced fecal output seen at 420 mg, but not at 300 mg. Reduced body weight gain at 420/300 mg during first 5-6 weeks of treatment. Transient reductions in erythrocyte count (females only), hemoglobin concentration and hematocrit and an increase in reticulocyte count at 420 mg, but these changes not seen at 300 mg. Increased liver weight and hepatocellular hypertrophy seen at 300 mg, with some evidence of an effect at lower dosages. Ultrastructural liver changes included slightly swollen mitochondria, decreased rough endoplasmic reticulum and an increase in lysosomes at 300 mg. Slight increases in serum alanine aminotransferase and triglycerides probably related to the liver changes.

Key: † = Initially 420 mg/kg/day, but reduced to 300 mg/kg/day on day 36 due to unacceptable toxicity.

Lamivudine:

In repeat dose toxicity studies, lamivudine was very well tolerated in the rat at oral doses up to 2,000 mg/kg b.i.d. for 6 months. Treatment related effects were restricted to minor hematological (mainly red cell parameters), clinical chemistry and urinalysis changes, and the mucosal hyperplasia of the cecum (in the 6 month study). The no (toxicologically important) effect level was 450 mg/kg b.i.d.

In the dog, oral doses of lamivudine 1,500 mg/kg b.i.d. in males and 1,000 mg/kg b.i.d. in females for a period of 12 months were well tolerated. Treatment related changes included reductions in red cell counts at all dose levels, associated with increased MCV and MCH, and reductions in total leucocyte, neutrophil and lymphocyte counts in high-dose animals, but with no effect on bone marrow cytology. Deaths were seen in females dosed with 1,500 mg/kg b.i.d. in a 3 month study but not in a 12 month study, using a dose of 1,000 mg/kg b.i.d.

When administered orally for one month, at a dose of 1,000 mg/kg b.i.d., lamivudine demonstrated low hematotoxic potential in the mouse, and did not significantly enhance the hematotoxicity of zidovudine or interferon α .

Carcinogenicity and Mutagenicity

Neither abacavir nor lamivudine was 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.

Abacavir:

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

The majority of these tumours occurred at the highest abacavir dose of 330 mg/kg/day in mice and 600 mg/kg/day in rats. These dose levels were equivalent to 24 to 33 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg. This is equivalent to six times the expected human systemic exposure. There is no structural counterpart for this gland in humans.

Reductions in survival and body weight in rats at 600 mg/kg/day resulted in the early discontinuation of dosing in Weeks 84 (males) and 100 (females). Survival in mice was also reduced at 330 mg/kg/day, resulting in the early discontinuation of dosing of males in Week 98.

While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

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 an *in vitro* cytogenetic study performed in human lymphocytes, abacavir induced chromosomal aberrations following exposure at 2,800 and 3,200 µg/mL for 3 hours in the presence of metabolic activation and after exposure at 100 and 125 µg/mL for 50.3 hours in the absence of metabolic activation. The abacavir concentrations at which evidence of genotoxicity was seen *in vitro* were at least 33 times higher than the expected maximum human blood level. In an *in vitro* mouse bone marrow micronucleus test, there was a small (2.3 fold) increase in the number of micronucleated polychromatic erythrocytes in males at 1,000 mg/kg. No significant increase was seen in bone marrow harvested from females. Findings in the micronucleus test were seen at systemic exposures (in terms of AUC) approximately nine times higher than exposure in humans at the therapeutic dose, and C_{max} values approximately 14 times higher than the maximum concentration in humans at the therapeutic dose.

No evidence of mutagenicity (with or without metabolic activation) was observed in bacterial mutagenicity assays at concentrations up to approximately 5,000 µg/plate. In a mutagenicity assay conducted in L5178Y mouse lymphoma cells, abacavir was weakly mutagenic following exposure at 250 µg/mL for 24 hours in the absence of metabolic activation. Abacavir was not mutagenic to L5178Y mouse lymphoma cells in a 3 hour exposure in the presence or absence of metabolic activation.

Lamivudine:

Traditional 24 month carcinogenicity studies using lamivudine have been conducted in mice and rats at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at recommended therapeutic doses. The following results should be noted. In mice, there appeared to be an increased incidence of histiocytic sarcoma in female mice treated with 180 mg/kg/day (6 of 60 mice) and 2,000 mg/kg/day (5 of 60 mice) when compared to control mice (two control groups with 1 of 60 and 2 of 60 mice). There did not appear to be an increased incidence in histiocytic sarcoma in female mice treated with 600 mg/kg/day (3 of 60 mice). It should be noted that the control incidence of this type of tumour in this strain of mice can be as high as 10%, similar to that found in the 180 and 2,000 mg/kg/day groups. In rats, there appeared to be an increased incidence of endometrial epithelial tumours in female rats treated with 3,000 mg/kg/day (5 of 55 rats) when compared to control rats (two control groups, each with 2 of 55 rats). There did not appear to be an increased incidence for endometrial tumours in rats treated with 1,000 mg/kg/day (2 of 55 rats) or 300 mg/kg/day (1 of 55 rats). It should be noted that there did not appear to be an increased incidence of any proliferative, non-neoplastic, epithelial lesions in treated female rats when compared to control rats, and the incidence of adenocarcinoma (5/55 or 9%) was only slightly higher than recorded controls at the laboratory where the study was conducted (4/50 or 8%). The statistical significance of the findings in mice and rats varied with the statistical analysis conducted, and therefore, the statistical and hence, the clinical significance of these findings are uncertain.

However, based on the similarity to historical control data, it was concluded that the results of long term carcinogenicity studies in mice and rats for lamivudine did not seem to show a carcinogenic potential relevant for humans.

Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg (approximately 65 times the recommended human dose based on body surface area comparisons).

Reproduction and Teratology

In reproductive toxicity studies in animals, abacavir and lamivudine were shown to cross the placenta. Fertility studies in the rat have shown that abacavir and lamivudine had no effect on male or female fertility.

Abacavir:

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at doses of up to 500 mg/kg/day.

Reproduction studies were performed in rats and rabbits at orally administered doses up to 1,000 mg/kg/day and 700 mg/kg/day, respectively. These doses in rats and rabbits achieved approximately 35 and 8.5 times, respectively, the exposure associated with the recommended human dose. In the rat, development toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed at the highest dose assessed. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg/day, a dose that was toxic to the parental generation. The offspring of female rats treated with abacavir at 500 mg/kg (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life.

This dose in rats achieved approximately 33 times the exposure with the usual human dose. In the rabbit, there was no evidence of drug related developmental toxicity and no increases in fetal malformations, at doses up to 700 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC).

Lamivudine:

A range of studies have been performed to assess the effects of repeated oral administration of lamivudine upon mammalian reproduction and development.

In a rat fertility study, except for a few minor changes in high dose (2,000 mg/kg b.i.d.) animals, the overall reproductive performance of the F₀ and F₁ generation animals, and the development of the F₁ and F₂ generation, was unaffected by treatment with lamivudine.

Lamivudine was not teratogenic in the rat or rabbit, at doses up to 2,000 mg/kg b.i.d. and 500 mg/kg b.i.d., respectively. In the rabbit a slight increase in the incidence of pre-implantation loss at doses 20 mg/kg b.i.d. and above indicates a possible early embryolethal effect. There was no such effect in the rat. These marginal effects occurred at relatively low doses, which produced plasma levels comparable to those achieved in patients.

In a peri-/post-natal/juvenile toxicity study in rats, some histological inflammatory changes at the ano-rectal junction and slight diffuse epithelial hyperplasia of the cecum were observed in dams and pups at the high-dose level. An increased incidence of urination upon handling was also seen in some offspring receiving 450 or 2,000 mg/kg. In addition, a reduction in testes weight was observed in juvenile males at 2,000 mg/kg which was associated with slight to moderate dilatation of the seminiferous tubules.

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PART III: CONSUMER INFORMATION**Pr KIVEXA[®]
abacavir (as abacavir sulfate)/lamivudine**

This leaflet is part III of a three-part "Product Monograph" published for KIVEXA[®] (abacavir sulfate/lamivudine) approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about KIVEXA[®]. Contact your doctor or pharmacist if you have any questions about the drug.

You may need to read this leaflet again. Please do not throw it away until you have finished treatment with KIVEXA[®].

ABOUT THIS MEDICATION**What the medication is used for:**

The Human Immunodeficiency Virus (HIV) is a retrovirus (a type of virus). Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

KIVEXA[®] belongs to a group of antiretroviral medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs), and are used in combination with other antiretrovirals to treat Human Immunodeficiency Virus (HIV) infection.

What it does:

KIVEXA[®] does not cure AIDS or kill the HIV virus, but helps to prevent further damage to the immune system by slowing down production of new viruses. At this time, there is no evidence that KIVEXA[®] will help you live longer or have fewer of the medical problems that are associated with HIV infection or AIDS. Because of this, you must be sure to be seen regularly by your health care provider.

When it should not be used:

KIVEXA[®] should not be taken if:

- you previously had an allergic reaction (hypersensitivity) to the active ingredient abacavir, which is also included in medicines called abacavir sulfate (ZIAGEN[®]) and abacavir sulfate/lamivudine/zidovudine (TRIZIVIR[®]).
- you previously had an allergic reaction to the active ingredient lamivudine (3TC[®]), lamivudine and zidovudine (COMBIVIR[®]) or abacavir sulfate/lamivudine/zidovudine (TRIZIVIR[®]) or any of the other ingredients found in KIVEXA[®] (see What the important nonmedicinal ingredients are).
- you have liver disease.

What the medicinal ingredient is:

KIVEXA[®] is a treatment that contains a fixed dose combination of two active ingredients that are currently available as separate medicines: ZIAGEN[®] (abacavir sulfate) and 3TC[®] (lamivudine). Each KIVEXA[®] tablet contains 600 mg of abacavir (as abacavir sulfate) and 300 mg lamivudine.

What the important nonmedicinal ingredients are:

Each KIVEXA[®] tablet contains the following nonmedicinal ingredients: hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, sodium starch glycolate, titanium dioxide and FD & C Yellow #6 Aluminum Lake.

What dosage forms it comes in:

KIVEXA[®] tablets are orange, film coated, modified, capsule shaped tablets, debossed with GS FC2 on one side and the other side plain, containing 600 mg abacavir as abacavir sulfate and 300 mg lamivudine. Available in blisters of 30 tablets.

WARNINGS AND PRECAUTIONS**Hypersensitivity Reaction**

Patients taking KIVEXA[®] may develop a hypersensitivity reaction (serious allergic reaction) which **can be life threatening** if you continue to take KIVEXA[®].

Your risk of this allergic reaction is much higher if you have a gene variation called HLA-B*501 than if you do not. Your doctor can determine with a blood test if you have this gene variation. Even if you don't have this gene variation, you may still experience this type of allergic reaction.

About 8 in every 100 patients who are treated with KIVEXA[®], develop a hypersensitivity reaction to the active ingredient abacavir.

You may be having a hypersensitivity reaction and you should stop taking KIVEXA[®] and contact your doctor immediately if you have two or more of the following sets of symptoms:

- **fever**
- **rash**
- **nausea, vomiting, diarrhea, or abdominal pain**
- **severe tiredness, achiness or general ill feeling**
- **sore throat, shortness of breath, or cough**

Other frequently observed symptoms of a hypersensitivity reaction include:

Frequent: nausea, vomiting, diarrhea, abdominal pain, shortness of breath, cough, headache and severe tiredness.

Other: sore throat, joint or muscle pain, swelling of the neck.

Occasional: inflammation of the eye (conjunctivitis), mouth ulcers, and low blood pressure.

The symptoms of this allergic reaction usually occur in the first six weeks of treatment with KIVEXA[®], but may occur at any time, and get worse with continued treatment.

A written list of these symptoms is on the Warning Card provided by your pharmacist. You should carry this Warning Card with you. **If you notice these symptoms while taking KIVEXA[®], stop taking KIVEXA[®] and call your doctor immediately.**

If you have had this reaction to KIVEXA[®], **never** take KIVEXA[®] or any other medicine containing abacavir (such as ZIAGEN[®] (abacavir sulfate) or TRIZIVIR[®] (abacavir sulfate/lamivudine/zidovudine) again, regardless of whether you have the HLA-B*5701 gene variation, as within hours you may experience a life threatening lowering of your blood pressure or death.

It is important if you have stopped taking KIVEXA[®] either on medical advice or because you think you are having side effects or due to other illness, that you **contact your doctor for advice** before restarting KIVEXA[®]. Your doctor will check whether any symptoms you had before stopping may be related to this hypersensitivity reaction. If your doctor has any doubt about this, you will be advised **never to take KIVEXA[®]** or any other medicine containing abacavir such as ZIAGEN[®] or TRIZIVIR[®] again.

You should return all of your unused KIVEXA[®] to the doctor or pharmacist for proper disposal.

Lactic acidosis (too much acid in the blood) and swollen and fatty liver (hepatomegaly with steatosis), including fatal cases, have been reported using nucleoside analogues alone or in combination. If you suffer symptoms (See Serious Side Effects Table), contact your doctor.

Pancreatitis (inflammation of the pancreas) has been observed in patients receiving abacavir and lamivudine (See Side Effects).

If you have a hepatitis B infection, you should not stop taking KIVEXA[®] without instructions from your doctor as your hepatitis may worsen or reoccur. Your doctor will monitor your conditions for several months after stopping treatment with KIVEXA[®].

Before you use KIVEXA[®], talk to your doctor or pharmacist:

- About all your medical conditions.
- If you have kidney or liver disease or hepatitis B.
- If you have had previous use of NRTI's.
- If you have been tested and know whether or not you have a gene variation HLA-B*5701.
- If you are pregnant or breastfeeding.
- About all the medicines you are taking including vitamins, herbal supplements and nonprescription drugs.

Other special warnings

The class of medicines to which KIVEXA[®] belongs (NRTIs) can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. Symptoms of lactic acidosis include feeling of weakness, loss of appetite, sudden unexplained weight loss, upset stomach and difficulty breathing or rapid breathing. This rare but serious side effect occurs more often in women. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with KIVEXA[®] your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

If you have hepatitis B infection, you should not stop KIVEXA[®] without instructions from your doctor, as you may have recurrence of your hepatitis. This may occur due to you suddenly stopping the active ingredient lamivudine in KIVEXA[®].

Some HIV medicines including abacavir may increase your 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.

KIVEXA[®] helps to control your condition but is not a cure for HIV infection. You will need to take it every day. Unless you suspect you are having an allergic reaction with KIVEXA[®], do not stop taking your medicine without first talking to your doctor.

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 KIVEXA[®].

Treatment with KIVEXA[®] 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.

Use of this medicine during pregnancy and breastfeeding:

If you are pregnant, or planning to become pregnant soon, you must inform your doctor before taking any medicine. The

safe use of KIVEXA[®] in pregnancy has not been established. Your doctor will decide whether you should continue to be treated with KIVEXA[®] if you are pregnant.

Babies and infants exposed to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) during pregnancy or labour show minor temporary increases in blood levels of lactate. The clinical importance of these temporary increases is unknown.

There have been very rare reports of disease that affect the nervous system such as delayed development and seizures.

These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies.

It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV from mother to child. Both of the active substances in KIVEXA[®] are likely to be found in breast milk.

You are recommended **not** to breastfeed your baby while taking KIVEXA[®].

The long term effects of KIVEXA[®] are not known.

Remember: This medicine is for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

INTERACTIONS WITH THIS MEDICATION

KIVEXA[®] should not be taken with:

- Zalcitabine (HIVID, ddc)
- 3TC[®] (lamivudine)
- COMBIVIR[®] (lamivudine and zidovudine)
- ZIAGEN[®] (abacavir sulfate)
- TRIZIVIR[®] (abacavir sulfate/ lamivudine/zidovudine)

Some of these medicines are already in KIVEXA[®].

It is important that you tell your doctor or pharmacist about all the medicines you are taking or have recently taken, including those you have bought yourself.

If you are taking methadone, your doctor may need to adjust your methadone dose, as abacavir increases the rate at which methadone leaves your body. This is unlikely to affect most methadone users.

In men, alcohol does increase the amount of abacavir in your blood. However, the meaning of this is unknown. This interaction has not been studied in women.

PROPER USE OF THIS MEDICATION

Usual dose:

Take KIVEXA[®] **exactly as your doctor has advised you, and try not to miss any doses.** The usual dose in adults (18 years and up) is one tablet once a day. The use of abacavir 600 mg once daily may be associated with a higher incidence of severe hypersensitivity reactions (serious allergic reaction). Swallow the tablet whole with water. KIVEXA[®] can be taken with or without food. KIVEXA[®] is a set (fixed) dose combination of abacavir sulfate and lamivudine, and therefore cannot be dose reduced. Therefore, KIVEXA[®] should not be used if you have to decrease the dose such as if you have kidney or liver problems or if you weigh less than 40 kg. If you are unsure about how to take it, ask your doctor or pharmacist. The use of KIVEXA[®] has not been studied in patients less than 18 years of age, in elderly patients (> 65 years) or patients with co-morbid conditions (e.g. liver or kidney problems).

Overdose:

If you accidentally take too much of your medicine you should **immediately** contact either your doctor, your pharmacist, hospital emergency department or the nearest poison control centre.

Missed Dose:

It is important to take this medicine as prescribed to ensure you get maximum benefit. If you forget to take a dose, 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.

If you stopped taking KIVEXA[®]:

If you stop taking KIVEXA[®] because of side effects or illness, you must contact your doctor before restarting to make sure that symptoms of a hypersensitivity reaction have not been missed. In some cases your doctor will ask you to restart KIVEXA[®] under direct medical supervision or in a place where you will be able to get ready access to medical care if needed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

A hypersensitivity reaction (serious allergic reaction) has been reported in about 8 in every 100 patients who have been treated with abacavir. This is described in the Serious Warnings and Precautions section on Hypersensitivity Reaction in the beginning of this leaflet. It is important that you read and understand the information about this serious reaction.

As KIVEXA[®] contains both abacavir sulfate and lamivudine, the side effects reported for each of these have been combined. The most common side effects (could affect at least one person in a 100) are nausea, vomiting, diarrhea, upper abdominal pain, headache, high temperature (fever), lethargy (unusual lack of energy), fatigue, loss of appetite, hair loss, joint and muscle pain, abacavir hypersensitivity (serious allergic reaction) and skin rash (without any other illness). **If these symptoms persist or become bothersome, contact your doctor.**

Very rare side effects (could affect less than one person in 10,000) are serious skin reactions and severe anemia.

Changes in body fat have been seen in patients taking antiretroviral therapy. These changes may include increased amount of fat on the upper back and neck ("buffalo hump"), breasts and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effect of these conditions is not known at this time.

Within the first few weeks of treatment with anti-HIV medicines, some people may develop inflammatory reactions (e.g. pain, redness, swelling, high temperature (fever)) which may resemble an infection and may be severe. It is thought that these reactions are caused by a recovery in the body's ability to fight infections, previously suppressed by HIV. The use of abacavir 600 mg once daily may be associated with a higher incidence of severe hypersensitivity reaction (serious allergic reaction). If you suffer from these symptoms, please discuss with your doctor.

Always tell your doctor or pharmacist about any new symptoms, even those not mentioned in this leaflet. If you feel ill in any other way that you do not understand, tell your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking KIVEXA[®], contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Serious Side Effect /Symptoms (2 or more of the following)	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Serious allergic reaction and the symptoms of fever, skin rash, nausea, vomiting, diarrhea, abdominal pain, severe tiredness, achiness, general ill-feeling, sore throat, shortness of breath, headache, loss of appetite, hair loss, joint and muscle pain.			X
Uncommon	Blood problems and symptoms such as anemia (lowered red blood cell count – resulting in fatigue, breathlessness), low white blood cell count (neutropenia – increasing chance of infection), reduced platelets (blood cells important for blood clotting – could increase chance of bruising) and increases in enzymes produced by the liver.			X

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Serious Side Effect /Symptoms (2 or more of the following)	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Pancreatitis (inflammation of the pancreas) and symptoms such as nausea, vomiting and abdominal pain.			X
Rare	Lactic acidosis (high level of acid in the blood) and symptoms such as weight loss, fatigue, malaise, abdominal pain, shortness of breath, severe hepatomegaly (swollen and enlarged liver) with symptoms of liver problems such as nausea, vomiting, abdominal pain, weakness and diarrhea.			X

HOW TO STORE IT

Store between 15 to 30°C.

As with all medicines, keep KIVEXA[®] out of the reach of children.

Do not take your medicine after the expiry date shown on the bottle, blister and/or the carton.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

www.viivhealthcare.com

or by contacting the sponsor, ViiV Healthcare ULC at:

8455 route Transcanadienne

Montréal, Quebec

H4S 1Z1

1-877-393-8448

This leaflet was prepared by ViiV Healthcare ULC.

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Warning Card

KIVEXA[®] (abacavir sulfate/lamivudine) Tablets

Patients taking KIVEXA[®] (abacavir sulfate/lamivudine) may develop a hypersensitivity reaction (a serious allergic reaction) which can be life threatening if you continue to take KIVEXA[®]. **If you notice two or more of the following sets of symptoms while taking KIVEXA[®], stop taking it and call your doctor immediately:**

	SYMPTOM(S)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, or abdominal pain
Group 4	Generally ill feeling, extreme tiredness or achiness
Group 5	Shortness of breath, cough or sore throat

If you have had this reaction to KIVEXA[®], **never take any medicine containing abacavir, such as TRIZIVIR[®] (abacavir sulfate/ lamivudine/zidovudine) or ZIAGEN[®] (abacavir sulfate) again.** If you take **any medicine containing abacavir, such as KIVEXA[®], TRIZIVIR[®] or ZIAGEN[®] again, within hours** you may experience a **life threatening lowering of your blood pressure or death.**

Carry this card with you at all times.

You should return all of your unused KIVEXA[®] to your doctor or pharmacist for proper disposal.