PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**KIVEXA**

abacavir and lamivudine tablets, Manufacturer's Standard

600 mg abacavir (as abacavir sulfate) and 300 mg lamivudine, Oral

Antiretroviral Agent

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Date of Initial Approval:
JUL 25, 2005

Date of Revision:
MAY 18, 2023

Submission Control No: 271805

RECENT MAJOR LABEL CHANGES

3 Serious Warnings and Precautions Box	05/2021
7 Warnings and Precautions, Clinical Management of Abacavir HSRs	05/2021
7 Warnings and Precautions, Immune	05/2021
7 Warnings and Precautions, General	05/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics (< 18 years of age)

The safety and efficacy of KIVEXA has been established in adolescents and children weighing at least 25 kg (see 4 DOSAGE AND ADMINISTRATION).

The safety and efficacy of KIVEXA has not been established in pediatric patients weighing less than 25 kg. Health Canada has not authorized an indication for use of KIVEXA in pediatric patients weighing less than25 kg.

1.2 Geriatrics (≥ 65 years of age)

Clinical studies of KIVEXA did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of KIVEXA in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

2 CONTRAINDICATIONS

KIVEXA 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.
- who are positive for the HLA-B*5701 allele and patients with a prior history of a hypersensitivity reaction (HSR) to abacavir, or products containing abacavir, regardless of HLA-B*5701 status. Fatal HSRs have been associated with rechallenge of abacavir (see 7 WARNINGS AND PRECAUTIONS.
- with hepatic impairment, as KIVEXA is a fixed-dose combination and the dosage of the individual components cannot be adjusted (see 4 DOSAGE AND ADMINISTRATION).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Fatal Hypersensitivity Reactions to Abacavir**

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of KIVEXA (abacavir and lamivudine). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele (see *7 WARNINGS AND PRECAUTIONS*).

KIVEXA is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS). All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with KIVEXA or reinitiation of therapy with KIVEXA, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue KIVEXA immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible (see *2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS*).

Following a hypersensitivity reaction to KIVEXA, NEVER restart KIVEXA or any other abacavir-containing product because more severe symptoms, including death, can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity (see *7 WARNINGS AND PRECAUTIONS*).

- **Post-Treatment Exacerbations of Hepatitis B**

Severe acute exacerbations of hepatitis B have been reported in patients who are co- infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, one component of KIVEXA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue KIVEXA. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Screen for HLA-B*5701 Allele Prior to Initiating or Reinitiating Therapy with KIVEXA

  All patients should be screened for the HLA-B*5701 allele prior to initiating or reinitiating treatment with KIVEXA, unless patients have a previously documented HLA-B*5701 allele assessment. (see 2 CONTRAINDICATIONS and 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

- KIVEXA can be taken with or without food.
- Before prescribing KIVEXA tablets, pediatric patients should be assessed for the ability to swallow tablets.
- Because KIVEXA is a fixed dose tablet it should not be prescribed for patients requiring dosage adjustments, such as:

- pediatric patients who weigh less than 40 kg with renal impairment (creatinine clearance <50 mL/min)
- patients who weigh less than 25 kg
- patients with renal impairment (creatinine clearance < 30 mL/min) (see 7 WARNINGS AND PRECAUTIONS, Renal insufficiency)
- patients with mild hepatic impairment
- patients 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.

4.2 Recommended Dose and Dosage Adjustment

Adults, adolescents and children weighing at least 25 kg

The recommended dose of KIVEXA in adults, adolescents and children weighing at least 25 kg is one tablet once daily. One tablet contains 600 mg abacavir (as abacavir sulfate) and 300 mg lamivudine.

Pediatrics (< 18 years of age and weighing less than 25 kg)

KIVEXA is not recommended for the treatment of children and adolescents weighing less than 25 kg as the necessary dose adjustment cannot be made.

Geriatrics (≥ 65 years of age)

There are limited data available on the use of abacavir and lamivudine (KIVEXA) in patients aged 65 years and older. However, there is no evidence that elderly patients would differ in their response from adult patients less than 65 years of age. When treating elderly patients, consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, concomitant medicinal products or disease.

4.5 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.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

If overdosage occurs, the patient should be monitored, and standard supportive treatment applied as required.

Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance. General supportive measures are recommended.

It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 –Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablet/ 600 mg abacavir (as abacavir sulfate) and 300 mg lamivudine	hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polysorbate 80, sodium starch glycolate, titanium dioxide and FD & C Yellow #6 Aluminum Lake.

Each KIVEXA tablet contains 600 mg of abacavir (as 702 mg abacavir sulfate) and 300 mg lamivudine.

Dosage Forms

KIVEXA tablets are orange, film coated, modified, capsule shaped tablets, debossed with GS FC2 on one side and the other side plain.

Packaging

Supplied in blisters of 30 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS Box at the beginning of Part I: Health Professional Information.

General

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

KIVEXA is a fixed-dose combination of two nucleoside analogues, abacavir sulfate and lamivudine and should not be administered concomitantly with other products containing either abacavir or lamivudine (3TC, COMBIVIR, DELSTRIGO, DOVATO, ZIAGEN or TRIUMEQ) or emtricitabine containing products (ATRIPLA, BIKTARVY, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, SYMTUZA, EMTRIVA, STRIBILD or TRUVADA).

KIVEXA tablets contain sunset yellow aluminium lake which may cause allergic-type reactions.

Hypersensitivity Reactions to Abacavir

Abacavir is associated with a risk for HSR characterized by fever and/or rash with other symptoms indicating multi-organ involvement. HSR can be life-threatening, and in rare cases fatal, when not managed appropriately. The risk for abacavir HSR to occur is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele. See ***Clinical Management of Abacavir HSRs*** below for additional details.

Carcinogenesis and Mutagenesis

Carcinogenicity studies with abacavir in mice and rats showed an increase in malignant tumours 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 exposures equivalent to 24 to 33 times the expected systemic exposure in humans (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Mutagenicity).

Abacavir was not mutagenic in a bacterial mutagenicity assay but induced chromosomal aberrations *in vitro* and was mutagenic in the absence of metabolic activation in an L5178Y mouse lymphoma assay. In an *in vivo* mouse bone marrow micronucleus assay, abacavir was clastogenic in males at exposures ~9X higher than those in humans at the therapeutic dose (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Mutagenicity).

Cardiovascular

Several observational and epidemiological studies have reported an association with abacavir use and the risk of myocardial infarction. Meta-analyses of randomized controlled trials have observed no excess risk of myocardial infarction with abacavir use. To date, there is no established biological mechanism to explain a potential increase in risk. Overall, the available data from observational studies and from controlled clinical trials show inconsistency and therefore the evidence for a causal relationship between abacavir treatment and the risk of myocardial infarction is inconclusive.

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

Endocrine and Metabolism

Serum lipids and blood glucose

Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and lifestyle changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

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 nucleoside analogues alone or in combination, including abacavir and lamivudine and other antiretrovirals. 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).

Female sex and obesity may be risk factors. Caution should be exercised when administering KIVEXA or other nucleoside analogues, particularly to those with known risk factors for liver disease. However,

cases have also been reported in patients with no known risk factors. Treatment with KIVEXA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

Hepatic Insufficiency

KIVEXA is contraindicated in patients with hepatic impairment because KIVEXA is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If patients require a dose reduction due to hepatic impairment, separate preparations of abacavir and lamivudine should be administered (see CONTRAINDICATIONS2 CONTRAINDICATIONS and 4.1 Dosing Considerations).

Post-Treatment Exacerbations of Hepatitis B

Clinical study and marketed use of lamivudine have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If KIVEXA is discontinued in patients coinfected with HBV, periodic monitoring of both liver function tests and markers of HBV replication should be considered.

Patients with HBV and/or HCV Co-infection

The safety and efficacy of KIVEXA have not been established in subjects co-infected with Hepatitis B and/or Hepatitis C virus.

Pancreatitis

Pancreatitis has been observed in some patients receiving nucleoside analogues, including 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 8.5 Post-Market Adverse Reactions).

Clinical Management of Abacavir HSRs

All patients should be screened for the HLA-B*5701 allele prior to initiating or re-initiating treatment with KIVEXA, unless patients have a previously documented HLA-B*5701 allele assessment.

Do not use KIVEXA in HLA-B*5701-positive patients or in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen.

HLA-B*5701-negative patients may develop a HSR to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients. **Regardless of HLA-B*5701 status, permanently discontinue KIVEXA if HSR cannot be ruled out, even when other diagnoses are possible** (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, influenza; gastroenteritis; or reactions to other medications).

Restarting abacavir-containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.

NEVER restart KIVEXA or any other abacavir-containing product in patients who have stopped therapy with KIVEXA due to a HSR.

When therapy with KIVEXA has been discontinued for reasons other than symptoms of a HSR, and if reinitiation of KIVEXA or any other abacavir- containing product is under consideration, carefully

evaluate the reason for discontinuation of KIVEXA to ensure that the patient did not have symptoms of a HSR.

If HSR cannot be ruled out, **DO NOT** reintroduce KIVEXA or any other abacavir-containing product.

If symptoms consistent with abacavir HSR are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a HSR. Make patients aware that HSR can occur with reintroduction of KIVEXA or any other abacavir-containing product. Reintroduction should be attempted only if the potential benefit outweighs the risk and if medical care can be readily accessed by the patient or others in case an adverse reaction occurs.

Clinical Description of Abacavir HSRs

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

Almost all HSR to abacavir include fever and/or rash. Other signs and symptoms that have been observed as part of abacavir HSR may include, respiratory signs and symptoms (including, but not limited to pharyngitis, dyspnea or cough), and gastrointestinal symptoms (including, but not limited to, nausea, vomiting, diarrhea or abdominal pain). Importantly, such symptoms **may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.** Other frequently observed signs or symptoms of HSR may include, but are not limited to, generalized malaise, fatigue or achiness (see 8.5 Post-Market Adverse Reactions, Description of Abacavir Hypersensitivity Adverse Reactions). The symptoms related to this HSR worsen with continued therapy and **can be life-threatening**. These symptoms usually resolve upon discontinuation of the abacavir-containing product.

A warning card with information for the patient about this HSR is included as part of the KIVEXA outer pack label (see a copy of this card on the last page of this Product Monograph).

Immune

Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution inflammatory syndrome has been reported in HIV-infected patients treated with combination antiretroviral therapy, including KIVEXA. During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium-complex (MAC), cytomegalovirus (CMV), Pneumocystis jirovecii pneumonia (PCP), and tuberculosis (TB)), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, autoimmune hepatitis and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

Renal Insufficiency

KIVEXA is not recommended for use in patients with a creatinine clearance < 30 mL/min as KIVEXA is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If patients require a dose reduction due to renal impairment, separate preparations of abacavir and lamivudine should be administered (see 4.1 Dosing Considerations, and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency.

Patients with renal impairment (creatinine clearance 30 – 49 mL/min)

Adult patients with a creatinine clearance between 30 and 49 mL per min receiving KIVEXA may experience a 1.6- to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL per min. There are no safety data from randomized, controlled trials comparing KIVEXA to the individual components in patients with a creatinine clearance between 30 and 49 mL per min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of hematologic toxicities (neutropenia and anemia), although discontinuations due to neutropenia or anemia each occurred in <1% of subjects. Patients with a sustained creatinine clearance between 30 and 49 mL per min who receive KIVEXA should be monitored for hematologic toxicities. If new or worsening neutropenia or anemia develop, dose adjustment of lamivudine, per lamivudine prescribing information, is recommended. If lamivudine dose adjustment is indicated, KIVEXA should be discontinued and the individual components should be used to construct the treatment regimen.

7.1 Special Populations

7.1.1 Pregnant Women

KIVEXA has not been studied in pregnant women. Therefore, KIVEXA should not be used in pregnant women unless the potential benefits outweigh the potential risk to the fetus.

There have been 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. Findings of developmental toxicity were also observed in animal toxicology studies (see 16 NON-CLINICAL TOXICOLOGY).

There have also 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.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to ART (antiretroviral therapy), including KIVEXA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients:

http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

To date, the Antiretroviral Pregnancy Registry has received reports of over 2,000 exposures to abacavir during pregnancy resulting in live birth. These consist of over 800 exposures during the first trimester, over 1,100 exposures during the second/third trimester and included 27 and 32 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.1% (2.0, 4.4%) and in the second/third trimester, 2.7% (1.9, 3.9%). Among pregnant women in the reference population, the background rate of birth defects is 2.7%. There appears to be no association between abacavir and overall birth defects observed in the Antiretroviral Pregnancy Registry.

The Antiretroviral Pregnancy Registry has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth. These consist of over 4,200 exposures during the first trimester, over 6, 900 exposures during the second/third trimester and included 135 and 198 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.6, 3.7%) and in the

second/third trimester, 2.8% (2.4, 3.2%). Among pregnant women in the reference population, the background rate of birth defects is 2.7%. The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for lamivudine compared to the background rate.

7.1.2 Breast-feeding

HIV-1 infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Lamivudine is excreted in human milk at similar concentrations to those found in serum. Abacavir is also secreted in human breast milk at similar concentrations as plasma levels. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving KIVEXA.

7.1.3 Pediatrics (< 18 years of age)

KIVEXA is not recommended for the treatment of adolescents and children weighing less than 25 kg as the necessary dose adjustment cannot be made.

The safety and efficacy of KIVEXA has not been established in pediatric patients weighing less than 25 kg

7.1.4 Geriatrics (≥ 65 years of age)

Clinical studies of KIVEXA did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of KIVEXA in elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions are discussed in 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS sections:

- Serious and sometimes fatal hypersensitivity reaction (see **Hypersensitivity Reactions to Abacavir**)
- Lactic acidosis and severe hepatomegaly (see **Lactic Acidosis and Severe Hepatomegaly with Steatosis**)
- Post-treatment exacerbations of hepatitis (see **Post-Treatment Exacerbations of Hepatitis B**)
- Myocardial infarction (see **Cardiovascular**)
- Serum lipids and blood glucose (see **Endocrine and Metabolism**)
- Immune reconstitution inflammatory syndrome (see **Immune**)

8.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Therapy-Naive Adults

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily, are listed in Table 2.

Table 2 Treatment-emergent Adverse Reactions of at Least Moderate Intensity (Grades 2-4) and ≥5% Frequency in Treatment-Naïve Adults (CNA30021) Through 48 Weeks of Treatment

Adverse Event	Abacavir 600 mg q.d. plus Lamivudine plus Efavirenz (n = 384)	Abacavir 300 mg b.i.d. plus Lamivudine plus Efavirenz (n = 386)
Drug hypersensitivity[a]	9%	7%
Insomnia	7%	9%
Depression/Depressed mood	7%	7%
Headache/Migraine	5%	5%
Fatigue/Malaise	5%	8%
Dizziness/Vertigo	5%	5%
Nausea	5%	6%
Diarrhea[a]	5%	6%
Rash	5%	5%
Pyrexia	5%	3%
Abnormal dreams	4%	5%
Anxiety	3%	5%

[a]Subjects receiving abacavir 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared with subjects who received abacavir 300 mg twice daily. Five percent (5%) of subjects receiving abacavir 600 mg once daily had severe drug hypersensitivity reactions compared with 2% of subjects receiving abacavir 300 mg twice daily. Two percent (2%) of subjects receiving abacavir 600 mg once daily had severe diarrhea while none of the subjects receiving abacavir 300 mg twice daily had this event.

Other adverse reactions observed in clinical studies include neutropenia, anemia, thrombocytopenia, anorexia, hyperlactatemia, lactic acidosis, vomiting, pancreatitis, erythema multiforme, upper abdominal pain, transient rise in liver enzymes (AST, ALT, GGT), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN).

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

The safety of once daily compared with twice daily dosing of abacavir and lamivudine was assessed in the ARROW study (COL105677). No additional safety issues were identified in pediatric patients (n=669) receiving abacavir and lamivudine either once (n=336) or twice daily dosing compared to adults. Within this population, 104 pediatric patients weighing at least 25 kg received abacavir and lamivudine once daily as KIVEXA.

8.3 Less Common Clinical Trial Adverse Reactions

One event of Grade 4 hepatitis in the once daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

Laboratory abnormalities (Grades 3-4) in therapy-naive adults during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 3. Additional laboratory abnormalities observed in clinical trials of 3TC were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

Table 3 - Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024) Through 48 Weeks of Treatment

Grade 3/4 Laboratory Abnormalities	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Elevated CPK (>4 X ULN)	8%	8%
Elevated ALT (>5 X ULN)	6%	6%
Elevated AST (>5 X ULN)	6%	5%
Hypertriglyceridemia (>750 mg/dL)	6%	5%
Hyperamylasemia (>2 X ULN)	4%	5%
Neutropenia (ANC <750/mm^3)	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (Platelets <50,000/mm^3)	1%	<1%
Leukopenia (WBC ≤1,500/mm^3)	<1%	2%

ULN = Upper limit of normal
n = Number of subjects assessed

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, and/or KIVEXA.

8.5 Post-Market Adverse Reactions

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 these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abacavir

Endocrine/Metabolic: lactic acidosis (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic), hepatic steatosis

Digestive: pancreatitis

Immune System: Immune Reconstitution Inflammatory Syndrome (see 7 WARNINGS AND PRECAUTIONS, Immune)

Skin: rash, **erythema multiforme**, **Stevens-Johnson syndrome (SJS)** and **toxic epidermal necrolysis (TEN)** (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.

Lamivudine

Body as a whole: anaphylaxis, weakness

Hematological: pure red cell aplasia

Hemic and Lymphatic: anemia, lymphadenophathy, splenomegaly

Endocrine/Metabolic: lactic acidosis (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic), hyperlactatemia, hepatic steatosis, hyperglycemia

Nervous: paresthesia, peripheral neuropathy

Digestive: rises in serum amylase, pancreatitis, stomatitis

Immune System: Immune Reconstitution Inflammatory Syndrome (see 7 WARNINGS AND PRECAUTIONS, Immune)

Skin: alopecia, pruritus, urticaria

Musculoskeletal: muscle disorders including rarely rhabdomyolosis, arthralgia

Description of Abacavir Hypersensitivity Adverse Reactions

Hypersensitivity

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

As described in 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. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise**.**

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

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is usually more severe than on initial presentation, and may include life-threatening hypotension and death. Reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

For details of clinical management in the event of a suspected abacavir HSR (see 7 WARNINGS AND

PRECAUTIONS, Clinical Management of Abacavir HSRs).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

As KIVEXA contains abacavir and lamivudine, any interactions that have been identified with these agents individually may occur with KIVEXA. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine. Abacavir and lamivudine are not significantly metabolized by cytochrome P_{450} (CYP) enzymes (such as CYP2C9 or CYP2D6) nor do they induce this enzyme system. Lamivudine does not inhibit CYP enzymes. *In vitro* studies have shown that abacavir inhibits CYP1A1, shows limited potential to inhibit metabolism mediated by CYP3A4, and has been shown *in vitro* not to inhibit CYP2C9 or CYP2D6 enzymes. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolized by major CYP 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.

Effect of Abacavir on the Pharmacokinetics of Other Agents

In vitro, abacavir has been shown to inhibit CYP1A1, and to a limited degree CYP3A4. When coadministered with abacavir or abacavir-containing drugs, exposures to drugs that are substrates of CYP1A1 enzyme could increase.

In vitro, abacavir demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistant protein (BCRP) or P-glycoprotein (Pgp) and minimal inhibition of organic cation transporter 1 (OCT1), OCT2 and multidrug and toxin extrusion protein 2-K (MATE2-K). Abacavir is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Abacavir is an inhibitor of MATE1 *in vitro*, however abacavir has low potential to affect the plasma concentrations of MATE1 substrates at therapeutic drug exposures (up to 600 mg).

Effect of Other Agents on the Pharmacokinetics of Abacavir

In vitro, abacavir is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, MATE1, MATE2-K, Multidrug resistance-associated protein 2 (MRP2) or MRP4, therefore drugs that modulate these transporters are not expected to affect abacavir plasma concentrations.

Although abacavir is a substrate of BCRP and Pgp *in vitro*, clinical studies demonstrate no clinically significant changes in abacavir pharmacokinetics when co-administered with lopinavir/ritonavir (Pgp and BCRP inhibitors).

Effect of Lamivudine on the Pharmacokinetics of Other Agents

In vitro, lamivudine demonstrates no or weak inhibition of the drug transporters OATP1B1, OATP1B3, BCRP or Pgp, MATE1, MATE2-K or OCT3. Lamivudine is therefore not expected to affect the plasma concentrations of drugs that are substrates of these drug transporters.

Lamivudine is an inhibitor of OCT1 and OCT2 in vitro with IC50 values of 17 and 33 µM, respectively, however lamivudine has low potential to affect the plasma concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

Effect of Other Agents on the Pharmacokinetics of Lamivudine

Lamivudine is a substrate of MATE1, MATE2-K and OCT2 *in vitro*. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations, however this interaction is not considered clinically significant as no dose adjustment of lamivudine is needed.

Lamivudine is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

Lamivudine is a substrate of Pgp and BCRP, however due to its high bioavailability it is unlikely that these transporters play a significant role in the absorption of lamivudine. Therefore co-administration of drugs that are inhibitors of these efflux transporters is unlikely to affect the disposition and elimination of lamivudine.

9.4 Drug-Drug Interactions

No drug interaction studies have been conducted with KIVEXA. The drugs listed in the following table 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 4 Established or Potential Drug-Drug Interactions

Abacavir Drug Interactions		
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.
Riociguat	*In vitro*, abacavir inhibits CYP1A1. Coadministration of a single dose of riociguat (0.5 mg) to HIV-1–infected subjects receiving fixed-dose TRIUMEQ (abacavir/dolutegravir/lamivudine once daily) resulted in approximately 3-fold higher riociguat AUC(0-∞) compared with historical riociguat AUC(0-∞) reported in healthy subjects, which may increase the risk of riociguat adverse reactions.	KIVEXA and Adempas (riociguat) should be co-administered with caution. Riociguat dose may need to be reduced, consult the riociguat product labeling for dosing recommendations.

Lamivudine Drug Interactions		
Proper name	**Effect**	**Clinical comment**
Sorbitol	Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC_{∞}) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults.	When possible, avoid chronic coadministration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.
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 4 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 *Pneumocystis jiroveci* pneumonia (often referred to as PCP) and toxoplasmosis has not been studied.
Emtricitabine	Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited.	KIVEXA is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.

9.5 Drug-Food Interactions

KIVEXA can be taken with or without food (see 10 CLINICAL PHARMACOLOGY).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

KIVEXA is a fixed dose combination of two nucleoside analogues (abacavir and lamivudine). Abacavir is a carbocyclic synthetic nucleoside analogue of deoxyguanosine-5'-triphosphate and lamivudine is also a synthetic nucleoside analogue, an (-) enantiomer of a dideoxy analogue of cytidine. Both abacavir and lamivudine are metabolized sequentially by intracellular kinases to their respective triphosphate (TP), which are the active moieties (carbovir triphosphate (CBV-TP) for abacavir; and lamivudine triphospate

(L-TP) for lamivudine). Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs), and are potent, selective inhibitors of HIV-1 and HIV-2 replication in *vitro. In vitro* L-TP has an intracellular half life of approximately 10.5 to 15.5 hours. L-TP and CBV-TP are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). Inhibition of RT is via viral DNA chain termination after nucleoside analogue incorporation. CBV-TP and L-TP show significantly less affinity for host cell DNA polymerases and are weak inhibitors of mammalian α, β and γ-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 hours sampling period, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 hours, compared to the geometric mean abacavir plasma half-life in this study of 2.6 hours.

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 hours, compared to the plasma lamivudine half-life of 5 to 7 hours.

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 14 CLINICAL TRIALS).

10.3 Pharmacokinetics

KIVEXA 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).

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 µg/mL and the mean AUC_{∞} is 11.95 µg.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 µg/mL and the mean AUC_{24} is 8.87 µg.h/mL.

Effect of Food on Absorption

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.

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 µg/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 18 to 19 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 Populations and Conditions

Pediatrics:

Abacavir is rapidly and well absorbed from oral solution and tablet formulations when administered to children. Plasma abacavir exposure has been shown to be the same for both formulations when administered at the same dose. Children receiving abacavir oral solution according to the recommended dosage regimen achieve plasma abacavir exposure similar to adults. Children receiving abacavir oral tablets according to the recommended dosage regimen achieve higher plasma abacavir exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation. Pediatric pharmacokinetic studies have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose for both oral solution and tablet formulations.

The absolute bioavailability of lamivudine (approximately 58 to 66%) was lower and more variable in pediatric patients under 12 years of age. In children, administration of tablets delivered higher plasma lamivudine $AUC\infty$ and C_{max} than oral solution. Children receiving lamivudine oral solution according to the recommended dosage regimen achieve plasma lamivudine exposure within the range of values observed in adults. Children receiving lamivudine oral tablets according to the recommended dosage regimen achieve higher plasma lamivudine exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation and the tablet formulation has higher bioavailability (see 4 DOSAGE AND ADMINISTRATION). Pediatric pharmacokinetic studies with both oral solution and tablet formulations have demonstrated that once daily dosing provides equivalent AUC_{0-24} to twice daily dosing of the same total daily dose.

Hepatic Insufficiency:

Pharmacokinetic data has been obtained for abacavir and lamivudine alone. Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6) 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 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 in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

Renal Insufficiency:

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 < 30 mL/min; therefore the separate preparation of lamivudine (3TC) should be used to treat these patients.

11 STORAGE, STABILITY AND DISPOSAL

Store KIVEXA tablets between 15 to 30°C.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

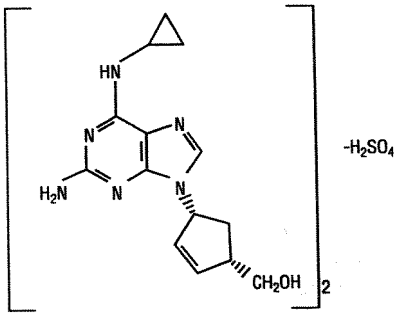
Drug Substance

Proper name: abacavir sulfate

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

Molecular formula and molecular mass: $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$, 670.76

Structural formula:



Physicochemical properties:

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

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

pKa: The pK_a for abacavir have been determined by UV spectroscopy at 25°C as follows: $pK_1 = 0.4$, $pK_2 = 5.06$.

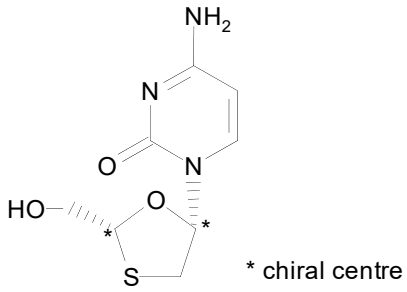
Drug Substance

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:

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

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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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 10.3 Pharmacokinetics). The clinical efficacy of antiretroviral combination therapy containing abacavir plus lamivudine, administered once or twice daily, has been confirmed in the study below.

Study Results

Therapy-Naive Adults

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 ≤ 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 5.

Table 5 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		
≤ 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.

Pediatrics

ARROW (COL105677) was a 5-year, randomized, multi centre trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric patients. HIV-1 infected, treatment-naive subjects aged 3 months to 17 years were enrolled and treated with first-line regimen containing 3TC and abacavir, dosed twice daily according to World Health Organization recommendations. After 36 weeks on treatment, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once daily with twice daily dosing of 3TC and abacavir, in combination with a third antiretroviral drug for an additional 96 weeks. Subjects randomized to receive once daily dosing (n = 336) and who weighed at least 25 kg received abacavir 600 mg and lamivudine 300 mg, as either the single entities or as KIVEXA. During the treatment period, 104 subjects took KIVEXA for a median duration of 596 days.

Of the 1206 original subjects enrolled in the study, 669 participated in Randomization 3. Virologic suppression was not a requirement for participation: at baseline (following a minimum of 36 weeks of twice daily treatment), 76% of subjects in the twice daily cohort were virologically suppressed, compared with 71% of subjects in the once daily cohort.

The proportion of subjects with HIV-1 RNA of less than 80 copies per mL through 96 weeks is shown in Table 6. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 6 Virologic response by HIV-1 RNA Copies Through 96 Weeks (Randomization of abacavir plus lamivudine Once Daily or Twice Daily Dosing - Snapshot Analysis)

	Twice Daily Dosing N = 333 n (%)	Once Daily Dosing N= 336 n (%)
Week 0 (After ≥36 Weeks on Treatment)		
Virological Response (<80 copies/mL)	250 (75)	237 (71)
Risk difference	-4.5% (95% CI -11.3% to +2.2%)	
Week 48		
Virological Response (<80 copies/mL)	242 (73)	233 (69)
Risk difference	-3.3% (95% CI -10.2% to +3.5%)	

	Twice Daily Dosing N = 333 n (%)	Once Daily Dosing N= 336 n (%)
Week 96		
Virological Response (<80 copies/mL)	232 (70)	226 (67)
Risk difference	-2.4% (95% CI -9.4% to +4.6%)	

The abacavir plus lamivudine once daily dosing group demonstrated non-inferiority to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 and including Week 96 (the secondary endpoint) all other thresholds tested (<200c/mL, <400c/mL, <1000c/mL). Virologic outcomes between treatment arms were comparable across baseline characteristics (gender, age, or viral load at randomization).

15 MICROBIOLOGY

In Vitro Activity

Abacavir

The *in vitro* anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1 IIIB 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 µM against HIV-1 IIIB, and was 0.26 ± 0.18 µM (1 µM = 0.28 µg/mL) against eight clinical isolates. The IC_{50} of abacavir against HIV-1 BaL varied from 0.07 to 1.0 µM. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

Lamivudine

The antiviral activity of lamivudine has been studied in combination with other antiretroviral compounds using HIV-1 infected MT-4 cells as the test system. No antagonistic effects were seen *in vitro* with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine).

Abacavir and Lamivudine

The antiviral activity of an equimolar mixture of abacavir and lamivudine in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine or efavirenz, or the protease inhibitors (PIs) amprenavir, indinavir, ritonavir, lopinavir, nelfinavir or saquinavir.

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 IC_{50} 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 ≤ 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.

[^{3}H]-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 [^{3}H]-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.

16 NON-CLINICAL TOXICOLOGY

With the exception of a negative in vivo rat micronucleus test, 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).

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. Slight increases in serum alanine aminotransferase and triglycerides were also observed in monkeys. Microscopically, slight centrilobular hepatocellular hypertrophy was seen in these animal species. 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. Occasional individual cell necrosis, pigment deposits in centrilobular hepatocyte and Kupffer cells were seen in mice and rats. Additional changes observed in toxicity studies included slight alterations in cholesterol, albumin and/or total protein in mice and/or rats and transient reductions in hematology parameters in monkeys. Clinical observations of toxicity (including emesis, hunched posture, hypoactivity, decreased appetite, and abnormal feces) occurred in monkeys administered high doses of abacavir daily for 12 months.

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 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.

Abacavir and Lamivudine in Combination

The results of an in vivo rat micronucleus test with abacavir and lamivudine in combination were negative. For each compound at the maximum dose (2000 mg/kg) mean systemic exposures were C_{max}: 75 and 28 μg/mL and AUC: 1185 and 377 μg.h/mL for abacavir and lamivudine, respectively.

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 vivo 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. 3TC (tablets, 300 mg and 150 mg; oral solution, 10 mg/mL; lamivudine), submission control #226212, Product Monograph, ViiV Healthcare ULC. (July 3, 2019)
2. ZIAGEN (tablets, 300 mg; oral solution 20 mg/ml; abacavir), submission control #243476 Product Monograph, ViiV Healthcare ULC. (January 20, 2021)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]KIVEXA
600 mg abacavir / 300 mg lamivudine

Read this carefully before you start taking **KIVEXA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KIVEXA**.

Serious Warnings and Precautions

Hepatitis B Infections

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

Hypersensitivity Reaction

You should be screened for the HLA-B*5701 gene variation prior to starting or re-starting treatment with KIVEXA, unless you have been screened previously and this is documented. Patients who have the HLA-B*5701 gene variation have a high risk of developing a hypersensitivity reaction (serious allergic reaction) to abacavir, which is in the drug KIVEXA. This hypersensitivity reaction **can be life threatening** if you continue to take KIVEXA.

If you get two or more of the following groups of symptoms while taking KIVEXA contact your healthcare professional immediately to find out if you should stop taking KIVEXA:

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

A list of these symptoms is on the Warning Card provided by your pharmacist. You should carry this Warning Card with you at all times. **If you notice these symptoms while taking KIVEXA, call your healthcare professional immediately. Your healthcare professional may advise you to stop taking KIVEXA.**

If you stop KIVEXA because of a serious allergic reaction, never take KIVEXA or any other medicine containing abacavir (such as ZIAGEN or TRIUMEQ) again, regardless of whether you have the HLA-B*5701 gene variation or not. Within hours you may experience a life threatening lowering of your blood pressure or death. If you stop KIVEXA for any other reason, even for a few days, and you are not allergic to KIVEXA, talk with your healthcare professional before taking it again. Taking KIVEXA again may cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take KIVEXA, again, start taking it when you are around medical help or people who can call a healthcare professional if you need one.

Occasionally, reactions have developed in people who start taking abacavir again, and had only one symptom on the Warning Card before they stopped taking it.

If you are hypersensitive to KIVEXA, return all your unused KIVEXA tablets for safe disposal. Ask your healthcare professional or pharmacist for advice.

What is KIVEXA used for?

KIVEXA is a medicine used in combination with other antiretrovirals to treat Human Immunodeficiency Virus (HIV) infection.

How does KIVEXA work?

KIVEXA contains the active ingredients abacavir sulfate and lamivudine. These belong to a group of anti-retroviral medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs), which are used to treat HIV infection.

KIVEXA does not cure HIV; it reduces the amount of virus in your body, and keeps it at a low level. It also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body fight infection. You must be sure to be seen regularly by your health care provider.

What are the ingredients in KIVEXA?

Medicinal ingredients: 600 mg of abacavir (as abacavir sulfate) and 300 mg lamivudine.

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.

KIVEXA comes in the following dosage forms:

600 mg abacavir /300 mg lamivudine fixed dose combination tablets.

Do not use KIVEXA if:

- you previously had an allergic reaction (hypersensitivity) to the active ingredient abacavir, which is also included in medicines called ZIAGEN and TRIUMEQ (see **What are the ingredients in KIVEXA**).
- you previously had an allergic reaction to the active ingredient lamivudine which is included in medicines called 3TC, COMBIVIR or any of the other ingredients found in KIVEXA (see **What are the ingredients in KIVEXA**).
- you have the HLA-B* 5701 gene variation.
- you have liver disease.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KIVEXA. Talk about any health conditions or problems you may have, including if you:

- have kidney or liver disease (including hepatitis B or C)
- have previously taken any other NRTI class medicine
- have been tested and know whether or not you have a gene variation called HLA-B*5701

Other warnings you should know about:

KIVEXA can cause serious side effects, including:

- **Lactic Acidosis and Severe Liver Problems:** 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 problems you may also be more at risk of getting this condition.

- **Heart Attack:** Some HIV medicines including KIVEXA 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 healthcare professional.
- **Risk of Infections:** You may continue to develop other infections and other illnesses associated with HIV while you are taking KIVEXA. You should therefore keep in regular contact with your healthcare professional.
- **Immune Reconstitution Inflammatory Syndrome:** Changes to your immune system can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

  Autoimmune disorders happen when the immune system attacks healthy body tissue. This may happen after you start taking medicines for HIV infection. Examples of this include Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders may occur many months after the start of treatment.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Blood Tests:

Your blood sugar levels (glucose) or level of fats (lipids) in your blood may increase with HIV treatment. Your healthcare professional will decide when to do blood tests, to check for these and other side effects, and will interpret the results.

Pregnancy and Newborns:

If you are pregnant, or planning to become pregnant, talk to your healthcare professional before taking KIVEXA. It is not known if KIVEXA is safe to use during pregnancy. Your healthcare professional will decide whether you should continue to take KIVEXA if you are pregnant. If you are pregnant and taking KIVEXA to prevent passing HIV to your unborn baby continue to follow your healthcare professionals' recommendations. If you have questions about the risks to your baby talk to your healthcare professional. If you take KIVEXA while you are pregnant, talk to your healthcare professional about how you can be included in the Antiretroviral Pregnancy Registry

Babies born to mothers who have taken Nucleoside Reverse Transcriptase Inhibitors (NRTIs) like KIVEXA during pregnancy or labour have had increased levels of lactate in their blood. The increases are usually temporary. There have also been very rare reports of problems that affect the baby's nervous system such as delayed development and seizures. The long-term effects of KIVEXA are not known.

Breastfeeding:

Do not breastfeed while taking ZIAGEN. There is a risk of passing HIV-1 to your baby if you breastfeed. KIVEXA can also be passed through breast milk and could harm your baby. If you are breastfeeding or planning to breastfeed, talk with your healthcare professional about the best way to feed your baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with KIVEXA:

- Emtricitabine, to treat HIV
- Methadone, to treat pain and drug addiction
- Retinoids, to treat skin conditions
- Riociguat, to treat high blood pressure
- Sorbitol-containing medicines (usually liquids)
- Trimethoprim sulphamethoxazole (co-trimoxazole), an antibiotic used to treat *Pneumocystis jiroveci* pneumonia (often referred to as PCP) or toxoplasmosis

KIVEXA should not be taken with:

- 3TC
- COMBIVIR
- ZIAGEN
- TRUVADA
- COMPLERA
- ATRIPLA
- EMTRIVA
- STRIBILD
- TRIUMEQ
- DELSTRIGO
- DOVATO
- DESCOVY
- GENVOYA
- ODEFSEY
- BIKTARVY
- SYMTUZA

Some of these medicines are already in KIVEXA.

How to take KIVEXA:

- Take KIVEXA **exactly as your healthcare professional has advised you, and try not to miss any doses**.
- KIVEXA can be taken with or without food.
- Swallow the tablet whole with water.
- For children, your healthcare professional will determine if the child is able to swallow the tablet.

If you stopped taking KIVEXA:

If you stop taking KIVEXA because of side effects or illness, you must contact your healthcare professional before restarting to make sure that symptoms of a hypersensitivity reaction have not been missed. In some cases your healthcare professional 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.

Usual dose:

The usual dose in adults, adolescents and children who weigh at least 25 kg is one tablet once a day.

Overdose:

If you think you have taken too much KIVEXA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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.

What are possible side effects from using KIVEXA?

These are not all the possible side effects you may feel when taking KIVEXA. If you experience any side effects not listed here, contact your healthcare professional.

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

KIVEXA contains both abacavir sulfate and lamivudine. The most common side effects for this combination are nausea, vomiting, diarrhea, upper abdominal pain, headache, high temperature (fever), lethargy (unusual lack of energy), fatigue, trouble sleeping, depression/depressed mood, loss of appetite, hair loss, joint and muscle pain, abacavir hypersensitivity (serious allergic reaction) and skin rash (without any other illness).

Other side effects (very rare) include serious skin reactions and severe anemia.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	In all cases	
Common			
Hypersensitivity to abacavir: Serious allergic reaction and 2 or more of the following symptoms: fever, skin rash, nausea, vomiting, diarrhea, abdominal pain, severe tiredness, achiness, general ill-feeling, sore throat, shortness of breath.		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 and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	In all cases	
Rare			
Pancreatitis (inflammation of the pancreas) and symptoms such as nausea, vomiting and abdominal pain.		X	
Lactic acidosis (high level of acid in the blood): 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	
Frequency Not Known			
Immune Reconstitution Inflammatory Syndrome and Autoimmune Disorders: fever, redness, rash or swelling, fatigue, joint or muscle pain, numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, chest pain or rapid heart rate, yellowing of the eyes and skin		X	
Heart Attack: chest pain or discomfort, pain in the jaw, neck or back or pain radiating down the left arm, shortness of breath, nausea, dizziness		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15 to 30°C.

As with all medicines, keep KIVEXA out of the reach and sight of children.

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

If you want more information about KIVEXA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.viivhealthcare.com, or by calling 1-877-393-8448.

This leaflet was prepared by ViiV Healthcare ULC

Last Revised: MAY 18, 2023

INFORMATION FOR PRESCRIBERS:

A copy of the warning card included with the KIVEXA carton is shown below,

WARNING CARD

KIVEXA (abacavir/lamivudine) Tablets

Patients taking KIVEXA (abacavir/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, contact your healthcare professional immediately to find out if you should stop taking KIVEXA:**

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

If you have already had this reaction to **KIVEXA**, **never take any medicine containing abacavir, such as ZIAGEN** (abacavir) **or TRIUMEQ** (dolutegravir/ abacavir/lamivudine) **again**. **If you take any medicine containing abacavir, such as KIVEXA, ZIAGEN or TRIUMEQ 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 healthcare professional or pharmacist for proper disposal.