SUMMARY OF PRODUCT CHARACTERISTICS

KIVEXA

Abacavir sulfate-lamivudine

QUALITATIVE AND QUANTITATIVE COMPOSITION

Orange, film-coated, modified capsule shaped tablets, debossed with GS FC2 on one side.

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

CLINICAL INFORMATION

Indications

KIVEXA is a combination of two nucleoside analogues (abacavir and lamivudine). It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and children weighing at least 25 kg.

Dosage and Administration

Pharmaceutical Form: Film-coated tablets

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

KIVEXA should not be administered to patients who weigh less than 25 kg because it is a fixed-dose tablet that cannot be dose reduced. Separate preparations of *ZIAGEN* and *EPIVIR* should be administered to patients weighing less than 25 kg.

KIVEXA can be taken with or without food.

KIVEXA is a fixed-dose tablet and should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance less than 30 ml/min. Separate preparations of abacavir (*ZIAGEN*) or lamivudine (*EPIVIR*) should be administered in cases where discontinuation or dose adjustment is indicated. In these cases the physician should refer to the individual product information for these medicinal products.

Populations

- **Adults and children weighing at least 25 kg**

The recommended dose of *KIVEXA* in adults and children weighing 25 kg or more is one tablet once daily.

- **Children weighing less than 25 kg**

KIVEXA is not recommended for treatment of children weighing less than 25 kg as the necessary dose adjustment cannot be made. Physicians should refer to the individual product information for lamivudine and abacavir.

- **Elderly**

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

- **Renal impairment**

Whilst no dosage adjustment of abacavir is necessary in patients with renal impairment, a dose reduction of lamivudine is required due to decreased clearance. Therefore *KIVEXA* is not recommended for use in patients with a creatinine clearance less than 30 ml/min (*see Pharmacokinetics*).

- **Hepatic impairment**

A dose reduction of abacavir may be required for patients with mild hepatic impairment (Child-Pugh grade A). As dose reduction is not possible with *KIVEXA,* the separate preparations of *ZIAGEN* and *EPIVIR* should be used when this is judged necessary. *KIVEXA* is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (*see Pharmacokinetics – Special Patient Populations*).

Contraindications

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

Warnings and Precautions

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

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

Abacavir is associated with a risk for hypersensitivity reactions (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.

The following should be adhered to:

- Testing for *HLA-B*5701* status should be considered before initiating abacavir treatment and also before re-starting abacavir treatment in patients of unknown *HLA-B*5701* status who have previously tolerated abacavir.

- *KIVEXA* is not recommended for use in patients with the *HLA-B*5701* allele, or in patients who have had a suspected abacavir HSR while taking any other medicinal product containing abacavir (e.g. *ZIAGEN, TRIZIVIR, TRIUMEQ*) regardless of *HLA-B*5701* status.

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

- In any patient treated with *KIVEXA,* the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making.

- ***KIVEXA* must be stopped without delay, even in the absence of the *HLA-B*5701* allele, if a HSR is suspected. Delay in stopping treatment with *KIVEXA* after the onset of hypersensitivity may result in a life-threatening reaction.**

- Patients who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining *KIVEXA* tablets in order to avoid restarting abacavir.

- **Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours, and may include life-threatening hypotension and death.**

- **Regardless of a patient's *HLA-B*5701* status, if therapy with any abacavir containing product has been discontinued for any reason and restarting abacavir therapy is under consideration, the reason for discontinuation must be established. If HSR cannot be ruled out, *KIVEXA* or any other medicinal product containing abacavir (e.g. *ZIAGEN, TRIZIVIR, TRIUMEQ*) must not be restarted.**

- If a hypersensitivity reaction is ruled out, patients may restart *KIVEXA.* Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re- initiating abacavir therapy (*see Section 4.8 Description of selected adverse reactions*). Patients must be made aware that HSR can occur with reintroduction of *KIVEXA* or any other medicinal product containing abacavir (e.g. *ZIAGEN, TRIZIVIR, TRIUMEQ*) and that reintroduction of *KIVEXA* or any other medicinal product containing abacavir (e.g. *ZIAGEN, TRIZIVIR, TRIUMEQ*) should be undertaken only if medical care can be readily accessed.

Clinical Description of abacavir HSR:

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

Almost all HSR to abacavir include fever and/or rash as part of the syndrome.

Other signs and symptoms that have been observed as part of abacavir HSR include respiratory and gastrointestinal symptoms, **which may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis** (*see Adverse Reactions, Description of Selected Adverse Reactions*). The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

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

Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering *KIVEXA*, particularly to those with known risk factors for liver disease. Treatment with *KIVEXA* should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

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

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

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

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

Myocardial Infarction- Several observational, epidemiological studies have reported an association with abacavir use and the risk of myocardial infarction. Meta-analyses of randomised 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. In totality 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, hyperlipidaemia, diabetes mellitus and smoking).

Excipients - *KIVEXA* tablets contain sunset yellow aluminium lake (E110) which may cause allergic-type reactions.

Interactions

As *KIVEXA* contains abacavir and lamivudine, any interactions that have been identified with these agents individually may occur with *KIVEXA*. Clinical studies have shown that there are no clinically significant interactions between abacavir and lamivudine. Abacavir and lamivudine are not significantly metabolised by cytochrome P_{450} enzymes (such as CYP 3A4, CYP 2C9 or CYP 2D6) nor do they induce this enzyme system. Lamivudine does not inhibit cytochrome P450 enzymes. Abacavir shows limited potential to inhibit metabolism mediated by CYP3A4 and has been shown *in vitro* not to inhibit CYP2C9 or CYP 2D6 enzymes. *In vitro* studies have shown that abacavir has potential to inhibit cytochrome P_{450} 1A1 (CYP1A1). Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P_{450} 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 demonstrates no or weak inhibition of the drug transporters organic anion transporter 1B1 (OATP1B1), OATP1B3, breast cancer resistance 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).

Interactions relevant to abacavir

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

Methadone - In a pharmacokinetic study, co-administration of 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 re-titration may be required.

Riociguat: In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose of riociguat (0.5 mg) to HIV patients receiving the combination of abacavir/dolutegravir/lamivudine (600mg/50mg/300mg once daily) led to an approximately three-fold higher riociguat $AUC_{(0-\infty)}$ when compared to historical riociguat $AUC_{(0-\infty)}$ reported in healthy subjects. Riociguat dose may need to be reduced, consult the riociguat product labeling for dosing recommendations.

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 uM, 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.

Interactions relevant to lamivudine

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. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (*see Dosage and Administration*). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* pneumonia 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. Lamivudine is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.

Pregnancy and Lactation

Pregnancy

There are no adequate and well-controlled trials in pregnant women and the safe use of abacavir, lamivudine or ALFDC in human pregnancy has not been established. Therefore administration of ALFDC in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the foetus.

Abacavir has been evaluated in the Antiretroviral Pregnancy Registry in over 2,000 women during pregnancy and postpartum. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for abacavir compared to the background rate (*see Clinical Studies*). Lamivudine has been evaluated in the Antiretroviral Pregnancy Registry in over 11,000 women during pregnancy and postpartum. Available human data from the Antiretroviral Pregnancy Registry do not show an increased risk of major birth defects for lamivudine compared to the background rate (*see Clinical Studies*).

Abacavir and lamivudine have been associated with findings in animal reproductive studies (*see Non-Clinical Information*).

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

Lactation

Health experts recommend that where possible HIV infected women do not breast-feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

In a study following repeat oral dose of either 150 mg lamivudine twice daily (given in combination with 300mg zidovudine twice daily) or 300 mg lamivudine twice daily, lamivudine was excreted in human breast milk (0.5 to 8.2 micrograms/ml) at similar concentrations to those found in serum. In other studies following repeat oral dose of 150 mg lamivudine twice daily (given either in combination with 300 mg zidovudine or as *COMBIVIR* or *TRIZIVIR*) the breast milk:maternal plasma ratio ranged between 0.6 and 3.3. In a study after repeat oral administration of 300 mg abacavir twice daily (given as *TRIZIVIR*), the breast milk:maternal plasma ratio was 0.9. No pharmacokinetic studies were conducted with abacavir once daily oral administration. Lamivudine median infant serum concentrations ranged between 18 and 28 ng/mL and were not detectable in one of the studies (assay sensitivity 7 ng/mL). Most infants (8 out of 9) had non-detectable levels of abacavir (assay sensitivity 16 ng/mL). Intracellular carbovir and lamivudine

triphosphate (active metabolites of abacavir and lamivudine) levels in breastfed infants were not measured therefore the clinical relevance of the serum concentrations of the parent compounds measured is unknown.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

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

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

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

Clinical Trial Data

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

Paediatric population

The safety database to support once daily dosing with *KIVEXA* in paediatric patients comes from the ARROW Trial (COL105677) in which 669 HIV-1 infected paediatric subjects received abacavir and lamivudine either once or twice daily (see Clinical Studies). Within this population, 104 HIV-1 infected paediatric subjects weighing at least 25 kg received abacavir and lamivudine as *KIVEXA* once daily. No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.

Postmarketing Data

In addition to the adverse events included from clinical trial data, the following adverse events listed in the table below have been identified during post-approval use of abacavir and lamivudine. These events have been chosen for inclusion due to a potential causal connection to abacavir and/or lamivudine.

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

[1]Lactic acidosis (*see Warnings and Precautions*)

Description of Selected Adverse Reactions

Hypersensitivity (*see also Warnings and Precautions*):

Abacavir hypersensitivity reaction (HSR) has been identified as a common adverse reaction with abacavir therapy. The signs and symptoms of this hypersensitivity reaction are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported in **at least 10% of patients** with a hypersensitivity reaction are in bold text.

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
Haematological:	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 Warnings and Precautions.

Overdose

Symptoms and Signs

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

Treatment

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Pharmacotherapeutic group - nucleoside reverse transcriptase inhibitor (NRTI) - ATC Code: J05A R02.

Mechanism of Action

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

In a study of 20 HIV-infected patients receiving abacavir 300 mg twice daily, with only one 300 mg dose taken prior to the 24 hour sampling period, the geometric mean terminal carbovir-TP intracellular half-life at steady-state was 20.6 hours, compared to the geometric mean abacavir plasma half-life in this study of 2.6 hours. 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 18 to 19 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 (CNA30021- *see Clinical Studies*).

Pharmacodynamic Effects

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. No antagonistic effects *in vitro* were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine, nevirapine, zalcitabine, and zidovudine).

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

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

Cross-resistance between abacavir or lamivudine and antiretrovirals from other classes e.g. protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI), is unlikely. Reduced susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors.

Clinical isolates with three or more mutations associated with NRTIs are unlikely to be susceptible to abacavir. Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine, stavudine, abacavir and tenofovir maintain their antiretroviral activities against lamivudine-resistant HIV-1 harbouring only the M184V mutation.

Pharmacokinetics

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

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

The pharmacokinetic properties of lamivudine and abacavir are described below.

Absorption

Abacavir and lamivudine are rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir and lamivudine in adults is 83% and 80 to 85% respectively. The mean time to maximal serum concentrations (t_{max}) is about 1.5 hours 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 micrograms/ml and the mean AUC_{∞} is 11.95 micrograms.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 micrograms/ml and the mean AUC_{24} is 8.87 micrograms.h/ml.

Distribution

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

Data show that abacavir and lamivudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). Studies with abacavir demonstrate a CSF to plasma AUC ratio of between 30 to 44%. The observed values of the peak concentrations are 9 fold greater than the IC_{50} of abacavir of 0.08 micrograms/ml or 0.26 micromolar when abacavir is given at 600 mg twice daily. The mean ratio of CSF/serum lamivudine concentrations 2 to 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 metabolised by the liver with less than 2% of the administered dose being renally excreted as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the administered dose. These metabolites are excreted in the urine.

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

Elimination

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

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 (greater than 70%) via the organic cationic transport system.

Special Patient Populations

Children - Abacavir is rapidly and well absorbed from oral solution and tablet formulations administered to children. Plasma abacavir exposure has been shown to be the same for both formulations when administered at the same dose. Children receiving abacavir oral solution according to the recommended dosage regimen achieve plasma abacavir exposure similar to adults. Children receiving abacavir oral tablets according to the recommended dosage regimen achieve higher plasma abacavir exposure than children receiving oral solution because higher mg/kg doses are administered with the tablet formulation. Paediatric pharmacokinetic studies have demonstrated that once daily dosing provides equivalent AUC_{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 paediatric patients under 12 years of age. In children, administration of tablets delivered higher plasma lamivudine AUC_{∞} 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 Dosage and Administration*). Paediatric pharmacokinetic studies with both oral solution and tablet formulations have demonstrated that once daily dosing provides equivalent AUC_{24} to twice daily dosing of the same total daily dose.

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

Dosage reduction of abacavir is likely to be required in patients with mild hepatic impairment. The separate preparation of abacavir (*ZIAGEN*) should therefore be used to

treat these patients. The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment. Plasma concentrations of abacavir are expected to be variable and substantially increased in these patients. *KIVEXA* is therefore not recommended in patients with moderate and severe hepatic impairment.

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

Renally impaired - Pharmacokinetic data have been obtained for abacavir and lamivudine alone. Abacavir is primarily metabolised by the liver, with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Studies with lamivudine show that plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Dose reduction is required for patients with creatinine clearance of less than 30 ml/min, therefore the separate preparation of lamivudine (*EPIVIR*) should be used to treat these patients.

Clinical Studies

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

In a multicentre, double-blind, controlled study (CNA30024), 654 HIV-infected, antiretroviral therapy-naïve patients were randomised to receive either abacavir 300 mg twice daily or zidovudine 300 mg twice daily, both in combination with lamivudine 150 mg twice daily and efavirenz 600 mg once daily. The duration of double-blind treatment was at least 48 weeks.

In the intent-to-treat (ITT) population, 70% of patients in the abacavir group, compared to 69% of patients in the zidovudine group, achieved a virologic response of plasma HIV-1 RNA less than or equal to 50 copies/ml by Week 48. Patients were stratified at baseline based on plasma HIV-1 RNA less than or equal to 100,000 copies/ml or greater than 100,000 copies/ml. The abacavir group was demonstrated to be non-inferior when compared to the zidovudine group in the overall and base-line viral load sub-groups. This study confirms the non-inferiority of a regimen containing abacavir plus lamivudine, compared to a more widely used regimen of zidovudine plus lamivudine.

A once daily regimen of abacavir and lamivudine was investigated in a multicentre, double-blind, controlled study (CNA30021) of 770 HIV-infected, therapy-naïve adults. They were randomised to receive either abacavir 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 less than or equal to 100,000 copies/ml or greater than 100,000 copies/ml. The duration of double-blind treatment was at least 48 weeks. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA <50 copies/ml at Week 48 ITT-Exposed Population		
Populations	**ABC once/day + 3TC + EFV (N = 384)**	**ABC twice/day + 3TC + EFV (N = 386)**
Sub-group by baseline RNA		
≤100,000 copies/ml	141/217 (65%)	145/217 (67%)
>100,000 copies/ml	112/167 (67%)	116/169 (69%)
Total population	253/384 (66%)	261/386 (68%)

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

Genotypic analysis was attempted for all subjects with virologic failure (confirmed HIV RNA greater than 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 greater than 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.

A comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least an additional 96 weeks. Within this population, 104 patients weighing at least 25 kg received 600 mg abacavir and 300 mg lamivudine as *KIVEXA* once daily, with a median duration of exposure of 596 days. The results are summarised in the table below:

Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis)

	Twice Daily n/N (%)	Once Daily n/N (%)
Week 0 (After ≥36 Weeks on Treatment)		
Plasma HIV-1 RNA <80 c/mL	250/331 (76)	237/335 (71)
Risk difference (once daily-twice daily)	-4.8% (95% CI -11.5% to +1.9%), p=0.16	
Week 48		
Plasma HIV-1 RNA <80 c/mL	242/331 (73)	236/330 (72)
Risk difference (once daily-twice daily)	-1.6% (95% CI -8.4% to +5.2%), p=0.65	
Week 96		
Plasma HIV-1 RNA <80 c/mL	234/326 (72)	230/331 (69)
Risk difference (once daily-twice daily)	-2.3% (95% CI -9.3% to +4.7%), p=0.52	

The abacavir/lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/mL, <400c/mL, <1000c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method.

Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry has received prospective 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 was 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.

Non-Clinical Information

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.

Mutagenicity and carcinogenicity

Neither abacavir nor lamivudine were mutagenic in bacterial tests, but like many nucleoside analogues they show activity in the *in vitro* mammalian tests such as the mouse lymphoma assay. This is consistent with the known activity of other nucleoside analogues. The results of an *in vivo* rat micronucleus test with abacavir and lamivudine in combination were negative.

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

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

Repeat-dose toxicity

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

Reproductive toxicology

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

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

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

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

PHARMACEUTICAL INFORMATION

List of Excipients

Tablet Core

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate.

Tablet Coating

Opadry Orange YS-1-13065-A containing:

Hypromellose (E464)

Titanium dioxide (E171)

Polyethylene glycol 400

Polysorbate 80 (E433)

Sunset yellow aluminium lake (E110) (*see Warnings and Precautions*).

Shelf Life

The expiry date is indicated on the packaging.

Storage

The storage conditions are detailed on the packaging.

Nature and Contents of Container

KIVEXA tablets are available in opaque white, polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) blister packs or in opaque white, PVC/PVdC child-resistant blister packs or white high density polyethylene (HDPE) bottles with child-resistant closures each containing 30 tablets.

Not all presentations are available in every country.

Incompatibilities

Not applicable.

Use and Handling

No special requirements.

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