AUSTRALIAN PRODUCT INFORMATION

KIVEXA (abacavir and lamivudine) film-coated tablets

Abacavir, a component of KIVEXA tablets, is associated with hypersensitivity reactions, which can be life-threatening, and in rare cases fatal. KIVEXA tablets, or any other medicinal product containing abacavir (TRIUMEQ, TRIZIVIR and ZIAGEN), MUST NEVER be restarted following a hypersensitivity reaction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

1 NAME OF THE MEDICINE

Abacavir (as sulfate) and lamivudine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KIVEXA is supplied as film-coated tablets each containing 600 mg of abacavir as abacavir sulfate and 300 mg lamivudine.

Abacavir sulfate is a white to off-white crystalline powder with a solubility of approximately 77 mg/mL in water at 25°C.

Lamivudine is a white to off-white crystalline solid which is highly soluble in water.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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

KIVEXA tablets can be taken with or without food.

KIVEXA tablets should not be prescribed for patients requiring dosage adjustments, such as those with creatinine clearance < 30 mL/min. Separate preparations of abacavir (ZIAGEN) or

lamivudine (3TC) should be administered in cases where discontinuation or dose adjustment is indicated. In these cases the physician should refer to the individual product information for these medicinal products.

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

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.

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

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 tablets are not recommended for use in patients with a creatinine clearance < 30 mL/min (see Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations).

Administration in subjects with moderate renal impairment

Patients with a creatinine clearance between 30 and 49 mL/min receiving KIVEXA may experience a 1.6 to 3.3- fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min (see Section 5.2 PHARMACOKINETIC PROPERTIES – Special populations). There are no safety data from randomised, controlled trials comparing KIVEXA to the individual components in patients with a creatinine clearance between 30 and 49 mL/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 haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in <1% of subjects. Other lamivudine-related adverse events (such as gastro-intestinal and hepatic disorders) may occur.

Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive KIVEXA should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with KIVEXA. KIVEXA should be discontinued and the individual components should be used to construct the treatment regimen.

Risks and benefits of using KIVEXA in patients with renal impairment should be assessed by a physician experienced in the management of HIV infection and discussed with the patient.

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 tablets, the separate preparations of abacavir and lamivudine should be used when this is judged to be necessary. KIVEXA is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh grade B or C) (see Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations).

4.3 CONTRAINDICATIONS

KIVEXA tablets are contra-indicated in patients with known hypersensitivity to abacavir or lamivudine, or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity – special warning
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 tablets.

Hypersensitivity to abacavir (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Hypersensitivity to abacavir is a multi-organ clinical syndrome which can occur at any time during treatment, but most often occurs within the first 6 weeks of therapy. Signs or symptom usually present in 2 or more of the following groups although hypersensitivity following the presentation of a single sign or symptom has been reported infrequently.

- fever
- rash
- gastrointestinal, including nausea, vomiting, diarrhoea, or abdominal pain
- constitutional, including generalized malaise, fatigue, or achiness
- respiratory, including dyspnoea, cough, or pharyngitis.

Hypersensitivity reactions may present similarly to pneumonia, bronchitis or pharyngitis, influenza-like illness or gastroenteritis.

- **Discontinue KIVEXA as soon as a hypersensitivity reaction is suspected.**
- **If hypersensitivity reaction cannot be ruled out, KIVEXA or any other medicinal product containing abacavir must not be restarted.**
- The risk is significantly increased for patients who test positive for the HLA-B*5701 allele. However, abacavir hypersensitivity reactions have been reported at a lower frequency in patients who do not carry this allele.
- **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 medicinal product containing abacavir.**
- Testing for HLA-B*5701 status is recommended before initiating abacavir treatment and also before re-starting abacavir treatment in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.
- The diagnosis of hypersensitivity reaction is based on clinical judgment. **If a hypersensitivity reaction is suspected, KIVEXA must be stopped without delay, even in the absence of the HLA-B*5701 allele.** Delay in stopping treatment with

abacavir after the onset of hypersensitivity may result in a life-threatening hypotension and death.

- Rarely, patients who have stopped abacavir for reasons other than symptoms of hypersensitivity reaction have also experienced life-threatening reactions within hours of re-initiating abacavir therapy. Therefore, if a hypersensitivity reaction is ruled out, the reintroduction of KIVEXA or any other abacavir-containing product is recommended only if medical care can be readily accessed.
- Each patient should be reminded to read the Consumer Medicine Information. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.
- Patients who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining KIVEXA tablets in order to avoid restarting 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 alone or in combination, including abacavir and lamivudine in the treatment of HIV infection. A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea).

Caution should be exercised when administering KIVEXA tablets, particularly to those with known risk factors for liver disease. Treatment with KIVEXA tablets 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).

Fat loss or fat gain
Fat loss or fat gain has been reported during combination antiretroviral therapy. The long term consequences of these events are currently unknown. A causal relationship has not been established.

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.

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

Transmission of infection
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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

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.

General
KIVEXA should not be taken with any other abacavir or lamivudine containing product (3TC, COMBIVIR, TRIUMEQ, TRIZIVIR, ZEFFIX, ZIAGEN).

As part of a triple drug-regimen, KIVEXA is generally recommended for use with antiretroviral agents from different pharmacological classes and not solely with other nucleoside/nucleotide reverse transcriptase inhibitors. This is based on results from randomised, double-blind, controlled studies in which the proportion of subjects with early virological failure (for example tenofovir, lamivudine and abacavir or tenofovir, lamivudine and didanosine) was higher in the triple nucleoside groups than in groups who received regimens involving two nucleosides in combination with an agent from a different pharmacological class. However, consideration needs to be given to a number of factors, including compliance, safety, toxicity and preservation of future treatment options, which also remain important when selecting an appropriate antiretroviral combination for a patient.

Therapy experienced patients:
In clinical trials patients with prolonged prior NRTI exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir or lamivudine and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients with prolonged prior NRTI exposure, or who have HIV-1 isolates containing multiple mutations conferring resistance to NRTIs (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Cross-resistance).

Use in hepatic impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations.

Use in renal impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations.

Use in the elderly
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use
KIVEXA is a fixed combination product not suitable for use in children aged <12 years who weigh less than 40 kg, for whom dosage recommendations vary based on body weight.

Effects on laboratory tests
See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Table 2.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As KIVEXA tablets contain abacavir and lamivudine, any interactions that have been identified with these agents individually may occur with KIVEXA tablets. 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 i*n 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 (600 mg/50 mg/300 mg once daily) led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy subjects. Riociguat dose may need to be reduced, consult the riociguat product labeling for dosing recommendations and for interactions observed in patients receiving highly active antiretroviral therapy.

Retinoids: Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

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 IC_{50} 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% (9 - 20%), 32% (28 - 37%), and 36% (32 - 41%) in lamivudine exposure (AUC_{∞}) and 28% (20 - 34%), 52% (47 - 57%), and 55% (50 - 59%) 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. Administration of lamivudine in patients with renal impairment should be assessed carefully. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis carinii* 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Abacavir had no adverse effects on the mating performance or fertility of male and female rats at oral doses of up to 427 mg/kg per day, a dose expected to produce exposures approximately 30-fold higher than that in humans at the therapeutic dose based on AUC. Orally administered lamivudine (up to 70 times anticipated clinical exposure based on C_{max}) have shown evidence of impairment of fertility in male and female rats.

There are no data on the affect of abacavir or lamivudine on human female fertility.

Use in pregnancy
(Category B3)
There are no adequate and well-controlled studies in pregnant women and the safe use of abacavir, lamivudine or KIVEXA in human pregnancy has not been established. Therefore, administration of KIVEXA 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. 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. 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.

Lamivudine has been evaluated in the Antiretroviral Pregnancy Registry. 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. 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.

There is no data available on the treatment with a combination of abacavir, and lamivudine in animals. In reproductive studies in animals, abacavir and lamivudine were shown to cross the placenta.

Studies in pregnant rats showed that abacavir is transferred to the foetus through the placenta. Developmental toxicity (depressed foetal body weight and reduced crown-rump length) and increased incidences of foetal anasarca and skeletal malformations were observed when rats were treated with abacavir at doses of 648 mg/kg during organogenesis (approximately 35 times the human exposure at the recommended dose, based on AUC). In a fertility study, evidence of toxicity to the developing embryo and foetuses (increased resorptions, decreased foetal body weights) occurred only at 427 mg/kg per day. The offspring of female rats treated with abacavir at 427 mg/kg (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in foetal malformations at doses up to 453 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC).

Lamivudine caused an increase in early embryonic deaths in the rabbit at exposures (based on C_{max} and AUC) less than the maximum anticipated clinical exposure. Lamivudine was not teratogenic in rats and rabbits with exposure (based on C_{max}) up to 40 and 36 times respectively those observed in humans at the clinical dosage.

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.

Use in lactation
No studies have been carried out to determine the effects of the combination of abacavir and lamivudine in lactating animals.

Abacavir and its metabolites are excreted into the milk of lactating rats. A study in lactating rats showed that the concentration of lamivudine in milk was more than four times higher than that in maternal plasma.

Excretion of abacavir and lamivudine in breast milk has been reported in clinical studies, resulting in sub-therapeutic infant plasma levels.

There is no data available on the safety of abacavir and/or lamivudine administered to babies less than three months old.

Breast feeding is not advised because of the potential for HIV transmission from mother to child, and the potential risk of adverse events due to antiretroviral drug excretion in breast milk.

In settings where formula feeding is unsafe or unavailable, the World Health Organisation has provided Guidelines.

4.7 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 tablets should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

KIVEXA tablets contain abacavir and lamivudine, therefore adverse events would be expected to be similar to those experienced by patients on separate preparations of lamivudine and abacavir. For many of the adverse events listed it is unclear whether they are related to specific antiretroviral agents, or the wide range of other medications taken by HIV-infected patients, or whether they are a result of the underlying disease process.

Description of selected adverse effects
Hypersensitivity to abacavir (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Clinical trial data

Table 1 lists the most common adverse events, occurring at an incidence of 5% or more, reported in the controlled pivotal clinical trial CNA30021, irrespective of the investigator's assessment of possible relationship to the study drug:

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 tablets have 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Table 1: Most Common (Greater than or equal to 5% Incidence) Grade 2 to 4 Adverse Events (Safety Population - CNA30021)

Adverse Event	**ABC once/day N=384 n (%)**	**ABC twice/day N=386 n (%)**
Subjects with ANY Grade 2 to 4 AE	267 (70%)	276 (72%)
Drug hypersensitivity	35 (9%)	27 (7%)
Insomnia	26 (7%)	36 (9%)
Depression	25 (7%)	26 (7%)
Diarrhea	21 (5%)	25 (6%)
Nausea	21 (5%)	25 (6%)
Headache	21 (5%)	21 (5%)
Rash	21 (5%)	19 (5%)
Fatigue	20 (5%)	29 (8%)
Dizziness	19 (5%)	19 (5%)
Pyrexia	19 (5%)	13 (3%)
Abnormal dreams	15 (4%)	19 (5%)
Anxiety	12 (3%)	20 (5%)

Table 2: Grade 3 to 4 Treatment Emergent Laboratory Abnormalities (Safety Population - CNA30021)

Grade 3 and 4 Laboratory Abnormalities	**ABC once/day N=384 N(%)**			**ABC twice/day N=386 N(%)**		
Clinical Chemistry	**Gr 3**	**Gr 4**	**Gr 3-4**	**Gr 3**	**Gr 4**	**Gr 3-4**
Elevated ALT	14 (4%)	9 (2%)	23 (6%)	18 (5%)	6 (2%)	24 (6%)
Elevated AST	10 (3%)	13 (3%)	23 (6%)	9 (2%)	5 (1%)	14 (4%)
Alkaline phosphatase	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Amylase	13 (3%)	2 (<1%)	15 (4%)	12 (3%)	0	12 (3%)

Grade 3 and 4 Laboratory Abnormalities	ABC once/day N=384 N(%)			ABC twice/day N=386 N(%)		
Bilirubin	0	2 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
Creatine kinase	13 (3%)	31 (8%)	44 (12%)	13 (3%)	22 (6%)	35 (9%)
Creatinine	0	0	0	0	1 (<1%)	1 (<1%)
Glucose	4 (1%)	1 (<1%)	5 (1%)	5 (1%)	0	5 (1%)
Sodium	2 (<1%)	0	2 (<1%)	1 (<1%)	0	1 (<1%)
Triglycerides	13 (3%)	5 (1%)	18 (5%)	13 (3%)	8 (2%)	21 (6%)
Hematology						
Hemoglobin	0	1 (<1%)	1 (<1%)	0	0	0
Neutrophils absolute	6 (2%)	3 (<1%)	9 (2%)	4 (1%)	1 (<1%)	5 (1%)
Platelets	2 (<1%)	0	2 (<1%)	2 (<1%)	0	2 (<1%)
WBC	0	0	0	1 (<1%)	0	1 (<1%)

Postmarketing data

In addition to the adverse events included from clinical trial data, the following adverse events listed in Table 3 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.

Table 3: Adverse Events Identified Post Approval

Body system	Abacavir	Lamivudine
Blood and lymphatic systems disorders		Very rare: pure red cell aplasia
Metabolism and nutrition disorders	Common: hyperlactataemia Rare: lactic acidosis[1]	Common: hyperlactataemia Rare: lactic acidosis[1]
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]See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and signs

No specific symptoms or signs have been identified following acute overdose with abacavir

or lamivudine, apart from those listed as Adverse 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.

For information on the management of overdose, contact the Poisons Information Centre on 131 126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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. Similar intracellular kinetics are expected from abacavir 600 mg once daily. 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. 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 of this combination given once daily has been demonstrated in a pivotal clinical study (CNA30021 - See Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

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).

Resistance
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.

Genetic analysis of isolates from patients failing an abacavir-containing regimen demonstrated that 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. 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.

In a study of therapy-naive adults receiving abacavir 600 mg once daily (n = 384) or 300 mg twice daily (n = 386) in a background regimen of lamivudine 300 mg and efavirenz 600 mg once daily (Study CNA30021), there was a low overall incidence of virologic failure at 48 weeks 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. This resulted in a small sample size. Therefore, no firm conclusions could be drawn regarding differences in treatment emergent mutations between the two treatment groups. Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the abacavir- and lamivudine-associated resistance mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir/lamivudine once daily (56%, 10/18) and twice daily (40%, 8/20). L74V, Y115F and K65R were the other RT mutations observed in the study.

Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a > 2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13). Fifty-six percent (10/18) of the virologic failure isolates in the once-daily abacavir group compared to 41% (7/17) of the failure isolates in the twice-daily abacavir group had a > 2.5-fold decrease in lamivudine susceptibility with median-fold changes of 81 (range 0.79 to > 116) and 1.1 (range 0.68 to > 116) in the once-daily and twice-daily abacavir arms, respectively.

Cross-resistance

Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors. Viruses containing abacavir and lamivudine resistance-associated mutations, namely, M184V, L74V, Y115F and K65R, exhibit cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine *in vitro* and in patients. The M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine and the K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the L74V plus the M184V/I mutation, viruses with K65R with or without the M184V/I mutation, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

Clinical trials
Abacavir and lamivudine have been used as components of antiretroviral combination therapy in naïve and experienced patients. Combination therapy has included other antiretroviral agents of the same class or different classes, such as PIs and NNRTIs. Abacavir and lamivudine from KIVEXA tablets have been shown to be bioequivalent to abacavir and lamivudine when given separately (see Section 5.2 PHARMACOKINETIC PROPERTIES). The clinical efficacy of antiretroviral combination therapy containing abacavir plus lamivudine, administered once or twice daily has been confirmed in the studies described below.

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 ≤ 100,000 copies/mL or > 100,000 copies/mL. The duration of double-blind treatment was at least 48 weeks. The results are summarised in the Table 4.

Table 4: 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)	Point Estimate	95% CI*
Stratified			-1.7	-8.4, 4.9
Sub-group by baseline RNA				
≤100,000 copies/mL	141/217 (65%)	145/217 (67%)	-1.8	-10.8, 7.1
>100,000 copies/mL	112/167 (67%)	116/169 (69%)	-1.6	-11.6, 8.4
Total population	253/384 (66%)	261/386 (68%)		

* Confidence interval

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 were similar in the two treatment groups.

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

In the intent-to-treat (ITT) population, 70% of patients in the abacavir group, compared to 69% of patients in the zidovudine group, achieved a virologic response of plasma HIV-1 RNA ≤ 50 copies/mL by Week 48. Patients were stratified at baseline based on plasma HIV-1 RNA ≤ 100,000 copies/mL or > 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.

5.2 PHARMACOKINETIC PROPERTIES

KIVEXA tablets have been shown to be bioequivalent to abacavir and lamivudine administered separately. This was demonstrated in a single dose, 3-way crossover bioequivalence study (CAL10001) of KIVEXA tablets (fasted) versus 2 x 300 mg abacavir tablets plus 2 x 150 mg lamivudine tablets (fasted) versus KIVEXA tablets 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. Food did not alter the extent of systemic exposure to abacavir based on AUC, but C_{max} was decreased by approximately 24% compared to fasted conditions. These results indicate that KIVEXA tablets 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 80-85% respectively. The mean time to maximal serum concentrations (t_{max}) is about 1.5 hours and 1.0 hour 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.

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 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 (< 10%).

Excretion
The mean plasma 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 (> 70%) via the organic cationic transport system.

Special populations

Impaired hepatic function
Pharmacokinetic data has been obtained for abacavir and lamivudine separately. 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). 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. Abacavir is therefore not recommended in patients with moderate to severe impairment of hepatic function and KIVEXA tablets are therefore also not recommended in such patients.

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

Impaired renal function
Pharmacokinetic data have been obtained for abacavir and lamivudine separately. 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. Lamivudine requires dose adjustment in patients with creatinine clearance of < 30 mL/min; as KIVEXA cannot be dose adjusted it is not recommended in these patients and the separate preparation of lamivudine (3TC) should be used. For patients with creatinine clearance 30 -49mL/min taking 300mg lamivudine daily, an approximately two-fold (range 1.6-3.3) increase in exposure of lamivudine was predicted in pharmacokinetic modelling studies. (see Section 4.2 Dose and method of administration).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Abacavir was inactive in *in vitro* tests for gene mutation in bacteria but it showed clastogenic activity against human lymphocytes *in vitro* and in an *in vivo* mouse micronucleus test. 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. Abacavir was not mutagenic in bacterial mutagenicity assays.

Lamivudine was not active in a microbial mutagenicity screen but did induce mutations at the thymidine kinase locus of mouse lymphoma L5178Y cells without metabolic activation. Lamivudine was clastogenic in human peripheral blood lymphocytes *in vitro,* with or without metabolic activation. In rats, lamivudine did not cause chromosomal damage in bone marrow cells *in vivo* or cause DNA damage in primary hepatocytes.

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

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. Nonmalignant tumours occurred in the liver of mice and rats, Harderian gland of female mice, and thyroid gland of rats. In rats, there were also increased incidences of urothelial hyperplasia and urinary bladder tumours, associated with increased urinary calculi.

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.

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.

When lamivudine was administered orally to separate groups of rodents at doses up to 2000 times (mice and male rats) and 3000 (female rats) mg/kg/day, there was no evidence of a carcinogenic effect due to lamivudine in the mouse study. In the rat study there was an increased incidence of endometrial tumours at the highest dose (approximately 70 times the estimated human exposure at the recommended therapeutic dose of one tablet twice daily, based on AUC). However, the relationship of this increase to treatment is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

magnesium stearate
microcrystalline cellulose
sodium starch glycollate

Tablet coating

Opadry Orange YS-1-13065-A contains:

- hypromellose
- titanium dioxide
- macrogol 400
- polysorbate 80
- sunset yellow FCF aluminium lake.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

KIVEXA tablets are supplied in opaque white, polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) blister packs or in opaque white, PVC/PVdC child-resistant* blister packs. Each pack type contains 30 tablets.

*complies with European Standard *EN 14375:2003 Child-resistant Non-reclosable Packaging for Pharmaceutical Products - Requirements And Testing*.

Not all blister types may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

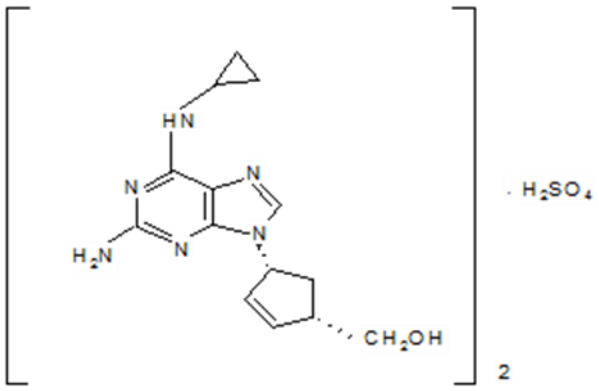
6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name of abacavir sulfate is (1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with 1S, 4R absolute configuration on the cyclopentene ring. It has a molecular formula of (C14H18N6O)2•H2SO4 and a molecular weight of 670.76 daltons.

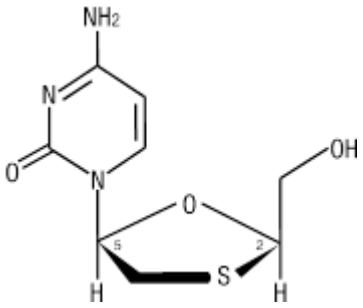
The chemical name of lamivudine is (2R,cis)-4-amino-1-[2- (hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine.

Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 daltons.

Chemical structure
Abacavir sulfate has the following structural formula:



Lamivudine has the following structural formula:



CAS number
188062-50-2 (abacavir sulfate); 134678-17-4 (lamivudine)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

ViiV Healthcare Pty Ltd
Level 4, 436 Johnston Street,
Abbotsford, Victoria, 3067
Australia

9 DATE OF FIRST APPROVAL

24 March 2005

10 DATE OF REVISION

14 March 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Inclusion of excipient allergy information.
	Update copyright statement

Version 17.0