ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIZIVIR 300 mg/150 mg/300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of abacavir (as sulfate), 150 mg lamivudine and 300 mg zidovudine.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Blue-green capsule-shaped film-coated tablets engraved with "GX LL1" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trizivir is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adults (see sections 4.4 and 5.1). This fixed combination replaces the three components (abacavir, lamivudine and zidovudine) used separately in similar doses. It is recommended that treatment is started with abacavir, lamivudine, and zidovudine separately for the first 6-8 weeks (see section 4.4). The choice of this fixed combination should be based not only on potential adherence criteria, but mainly on expected efficacy and risk related to the three nucleoside analogues.

The demonstration of the benefit of Trizivir is mainly based on results of studies performed in treatment naive patients or moderately antiretroviral experienced patients with non-advanced disease. In patients with high viral load (> 100,000 copies/ml) choice of therapy needs special consideration (see section 5.1).

Overall, the virologic suppression with this triple nucleoside regimen could be inferior to that obtained with other multitherapies notably including boosted Protease inhibitors or non nucleoside reverse transcriptase inhibitors, therefore the use of Trizivir should only be considered under special circumstances (e.g. co-infection with tuberculosis).

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin(see section 4.4). . Abacavir should not be used in patients known to carry the HLA-B*5701 allele.

4.2 Posology and method of administration

Posology

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

The recommended dose of Trizivir in adults (18 years and over) is one tablet twice daily.

Trizivir can be taken with or without food.

Where discontinuation of therapy with one of the active substances of Trizivir is indicated, or where dose reduction is necessary separate preparations of abacavir, lamivudine and zidovudine are available.

Special populations

Renal impairment

Whilst no dose adjustment of abacavir is necessary in patients with renal dysfunction, lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. Therefore, as dose adjustments of these may be necessary, it is recommended that separate preparations of abacavir, lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 ml/min). Physicians should refer to the individual summary of product characteristics of these medicinal products. Trizivir should not be administered to patients with end-stage renal disease (see sections 4.3 and 5.2).

Hepatic impairment

Trizivir is contraindicated in patients with hepatic impairment (see sections 4.3 and 5.2).

Elderly

No pharmacokinetic data are currently available in patients over 65 years of age. Special care is advised in this age group due to age associated changes such as the decrease in renal function and alteration of haematological parameters.

Paediatric population

The safety and efficacy of Trizivir in adolescents and children has not been established. No data are available.

Dose adjustments in patients with haematological adverse reactions

Dose adjustment of zidovudine may be necessary if the haemoglobin level falls below 9 g/dl or 5.59 mmol/l or the neutrophil count falls below 1.0 x 10^9/l (see sections 4.3 and 4.4). As dose adjustment of Trizivir is not possible, separate preparations of abacavir, lamivudine and zidovudine should be used. Physicians should refer to the individual summary of product characteristics of these medicinal products.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. See sections 4.4 and 4.8

Patients with end-stage renal disease.

Patients with hepatic impairment.

Due to the active substance zidovudine, Trizivir is contraindicated in patients with abnormally low neutrophil counts (< 0.75 x 10^9/l), or abnormally low haemoglobin levels (< 7.5 g/dl or 4.65 mmol/l) (see section 4.4).

4.4 Special warnings and precautions for use

The special warnings and precautions relevant to abacavir, lamivudine and zidovudine are included in this section. There are no additional precautions or warnings relevant to the combination Trizivir.

Hypersensitivity Reactions (see also section 4.8)***:***

Abacavir is associated with a risk for hypersensitivity reactions (HSR) (see section4.8) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for abacavir HSR to occur is high 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.

Therefore the following should be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- Trizivir should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen. (e.g. Kivexa, Ziagen, Triumeq)
- **Trizivir must be stopped without delay**, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Trizivir after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with Trizivir for reasons of a suspected HSR, Trizivir **or any other medicinal product containing abacavir** (e.g. Kivexa, Ziagen, Triumeq) **must never be re-initiated**.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.
- In order to avoid restarting abacavir patients who have experienced a suspected HSR should be instructed to dispose of their remaining Trizivir tablets

- *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. Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms **may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.**

The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

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). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Lactic acidosis

Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

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 reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These adverse reactions 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.

Lipodystrophy

CART has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these adverse reactions are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Haematological adverse reactions

Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving zidovudine. These occurred more frequently at higher zidovudine doses (1200-1500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with

advanced HIV disease. Haematological parameters should therefore be carefully monitored (see section 4.3) in patients receiving Trizivir. These haematological effects are not usually observed before four to six week's therapy. For patients with advanced symptomatic HIV disease, it is generally recommended that blood tests are performed at least every two weeks for the first three months of therapy and at least monthly thereafter.

In patients with early HIV disease haematological adverse reactions are infrequent. Depending on the overall condition of the patient, blood tests may be performed less often, for example every one to three months. Additionally, dose adjustment of zidovudine may be required if severe anaemia or myelosuppression occurs during treatment with Trizivir, or in patients with pre-existing bone marrow compromise e.g. haemoglobin < 9 g/dl (5.59 mmol/l) or neutrophil count < 1.0 x 10^9/l (see section 4.2). As dose adjustment of Trizivir is not possible separate preparations of zidovudine, abacavir and lamivudine should be used. Physicians should refer to the individual prescribing information for these medicinal products.

Pancreatitis

Cases of pancreatitis have occurred rarely in patients treated with abacavir, lamivudine and zidovudine. However, it is not clear whether these cases were due to treatment with these medicinal products or to the underlying HIV disease. Treatment with Trizivir should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Liver disease

If lamivudine is being used concomitantly for the treatment of HIV and HBV, additional information relating to the use of lamivudine in the treatment of hepatitis B infection is available in the Zeffix SmPC.

The safety and efficacy of Trizivir has not been established in patients with significant underlying liver disorders. Trizivir is contraindicated in patients with hepatic impairment (see section 4.3).

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

If Trizivir is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of both liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis (see Zeffix SmPC).

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Patients co-infected with hepatitis B or C virus

The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.5).

Children and adolescents

Because insufficient data are available, the use of Trizivir in children or adolescents is not recommended. In this patient population, hypersensitivity reactions are particularly difficult to identify.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens 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 CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients should be advised that Trizivir or any other antiretroviral therapy does not cure HIV infection and that they 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

Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Trizivir, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Transmission

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.

Drug Interactions:

To date there are insufficient data on the efficacy and safety of Trizivir given concomitantly with NNRTIs or PIs (see section 5.1).

Trizivir should not be taken with any other medicinal products containing lamivudine or medicinal products containing emtricitabine.

The concomitant use of stavudine with zidovudine should be avoided (see section 4.5).

The combination of lamivudine with cladribine is not-recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Trizivir contains abacavir, lamivudine and zidovudine, therefore any interactions identified for these individually are relevant to Trizivir. Clinical studies have shown that there are no clinically significant interactions between abacavir, lamivudine and zidovudine.

Abacavir is metabolised by UDP-glucuronyltransferase (UGT) enzymes and alcohol dehydrogenase; co-administration of inducers or inhibitors of UGT enzymes or with compounds eliminated through alcohol dehydrogenase could alter abacavir exposure. Zidovudine is primarily metabolised by UGT enzymes; co-administration of inducers or inhibitors of UGT enzymes could alter zidovudine exposure. Lamivudine is cleared renally. Active renal secretion of lamivudine in the urine is mediated through organic cation transporters (OCTs); co-administration of lamivudine with OCT inhibitors may increase lamivudine exposure.

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

Interaction studies have only been performed in adults. The list below should not be considered exhaustive but is representative of the classes studied.

Drugs by Therapeutic Area	**Interaction Geometric mean change (%) (Possible mechanism)**	**Recommendation concerning co-administration**
ANTIRETROVIRAL MEDICINAL PRODUCTS		
Didanosine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
Didanosine/Lamivudine	Interaction not studied.	
Didanosine/Zidovudine	Interaction not studied.	
Stavudine/Abacavir	Interaction not studied.	Combination not recommended.
Stavudine/Lamivudine	Interaction not studied.	
Stavudine/Zidovudine	In vitro antagonism of anti-HIV activity between stavudine and zidovudine could result in decreased efficacy of both drugs.	
ANTI-INFECTIVE PRODUCTS		
Atovaquone/Abacavir	Interaction not studied.	As only limited data available the clinical significance is unknown.
Atovaquone/Lamivudine	Interaction not studied.	
Atovaquone/Zidovudine (750 mg twice daily with food/200 mg thrice daily)	Zidovudine AUC ↑33% Atovaquone AUC ↔	
Clarithromycin/Abacavir	Interaction not studied.	Separate administration of Trizivir and clarithromycin by at least 2 hours
Clarithromycin/Lamivudine	Interaction not studied.	
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓12%	
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Abacavir	Interaction not studied.	No Trizivir dosage adjustment necessary, unless patient has

Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Lamivudine (160mg/800mg once daily for 5 days/300mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (organic cation transporter inhibition)	renal impairment (See Section 4.2). When concomitant administration with co-trimoxazole is warranted, patients should be monitored clinically. High doses of trimethoprim/ sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis have not been studied and should be avoided.
Trimethoprim/sulfamethoxazole (Co-trimoxazole)/Zidovudine	Interaction not studied.	
ANTIFUNGALS		
Fluconazole/Abacavir	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Fluconazole/Lamivudine	Interaction not studied.	
Fluconazole/Zidovudine (400 mg once daily/200 mg thrice daily)	Zidovudine AUC ↑74% (UGT inhibition)	
ANTIMYCOBACTERIALS		
Rifampicin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.

Drugs by Therapeutic Area	**Interaction Geometric mean change (%) (Possible mechanism)**	**Recommendation concerning co-administration**
Rifampicin/Lamivudine	Interaction not studied.	Insufficient data to recommend dosage adjustment.
Rifampicin/Zidovudine (600mg once daily/200 mg thrice daily)	Zidovudine AUC ↓48% (UGT induction)	
ANTICONVULSANTS		
Phenobarbital/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Phenobarbital/Lamivudine	Interaction not studied.	
Phenobarbital/Zidovudine	Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction.	

Phenytoin/Abacavir	Interaction not studied. Potential to slightly decrease abacavir plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment. Monitor phenytoin concentrations.
Phenytoin/Lamivudine	Interaction not studied.	
Phenytoin/Zidovudine	Phenytoin AUC ↑↓	
Valproic acid/Abacavir	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Valproic acid/Lamivudine	Interaction not studied.	
Valproic acid/Zidovudine (250 mg or 500 mg thrice daily/100 mg thrice daily)	Zidovudine AUC ↑80% (UGT inhibition)	
ANTIHISTAMINES (HISTAMINE H2 RECEPTOR ANTAGONISTS)		
Ranitidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
Ranitidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Ranitidine eliminated only in part by renal organic cation transport system.	
Ranitidine/Zidovudine	Interaction not studied	
Cimetidine/Abacavir	Interaction not studied.	No dosage adjustment necessary.
Cimetidine/Lamivudine	Interaction not studied. Clinically significant interaction unlikely. Cimetidine eliminated only in part by renal organic cation transport system.	
Cimetidine/Zidovudine	Interaction not studied.	

Drugs by Therapeutic Area	Interaction Geometric mean change (%) (Possible mechanism)	Recommendation concerning co-administration
CYTOTOXICS		
Cladribine/Lamivudine	Interaction not studied. *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine.	Therefore, the concomitant use of lamivudine with cladribine is not recommended (see section 4.4).
OPIOIDS		
Methadone/Abacavir (40 to 90mg once daily for 14 days/600mg single dose, then 600mg twice daily for 14 days)	Abacavir: AUC ↔ Cmax ↓35% Methadone: CL/F ↑22%	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8). Methadone dosage adjustment unlikely in majority of patients; occasionally methadone re-titration may be required.
Methadone/Lamivudine	Interaction not studied.	
Methadone/Zidovudine (30 to 90 mg once daily/200 mg every 4 hours)	Zidovudine AUC ↑43% Methadone AUC ↔	
RETINOIDS		
Retinoid compounds (e.g. isotretinoin)/Abacavir	Interaction not studied. Possible interaction given common pathway of elimination via alcohol dehydrogenase.	Insufficient data to recommend dosage adjustment.
Retinoid compounds (e.g. isotretinoin)/Lamivudine No drug interaction studies	Interaction not studied.	
Retinoid compounds (e.g. isotretinoin)/Zidovudine	Interaction not studied.	
URICOSURIC		
Probenecid/Abacavir	Interaction not studied.	As only limited data are available the clinical significance is not known. Monitor for signs of zidovudine toxicity (see section 4.8).
Probenecid/Lamivudine	Interaction not studied.	
Probenecid/Zidovudine (500 mg four times daily/2mg/kg thrice daily)	Zidovudine AUC ↑106% (UGT inhibition)	
MISCELLANEOUS		
Ethanol/Abacavir (0.7 g/kg single dose/600mg single dose)	Abacavir: AUC ↑41% Ethanol: AUC ↔ (Inhibition of alcohol dehydrogenase)	No dosage adjustment necessary.
Ethanol/Lamivudine	Interaction not studied.	
Ethanol/Zidovudine	Interaction not studied.	

Abbreviations: ↑ = Increase; ↓=decrease; ↔= no significant change; AUC=area under the concentration versus time curve; Cmax=maximum observed concentration; CL/F=apparent oral clearance

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine (see section 4.8). If concomitant therapy with Trizivir and any of these medicinal products is necessary then extra care should be taken in monitoring renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.

Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with cotrimoxazole (see interaction information above relating to lamivudine and co-trimoxazole), aerosolised pentamidine, pyrimethamine and acyclovir at doses used in prophylaxis.

4.6 Fertility, pregnancy and lactation

Pregnancy

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account. In the present case, the use in pregnant women of zidovudine, with subsequent treatment of the newborn infants, has been shown to reduce the rate of maternal-foetal transmission of HIV. There are no data on the use of Trizivir in pregnancy. A moderate amount of data on pregnant women taking the individual actives abacavir, lamivudine and zidovudine in combination indicates no malformative toxicity (more than 300 outcomes from first trimester exposures). A large amount of data on pregnant women taking lamivudine or zidovudine indicate no malformative toxicity (more than 3000 outcomes from first trimester exposure each, of which over 2000 outcomes involved exposure to both lamivudine and zidovudine). Moderate amount of data (more than 600 outcomes from first trimester) indicates no malformative toxicity for abacavir. The malformative risk is unlikely in humans based on the mentioned moderate amount of data.

The active ingredients of Trizivir may inhibit cellular DNA replication, zidovudine has been shown to be transplacental carcinogen in one animal study and abacavir has been shown to be carcinogenic in animal models (see section 5.3). The clinical relevance of these findings is unknown.

For patients co-infected with hepatitis who are being treated with a lamivudine containing medicinal product such as Trizivir and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.

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 (see section 4.4).

Breast-feeding

Abacavir and its metabolites are excreted into the milk of lactating rats. Abacavir is also excreted into human milk.

Based on more than 200 mother/child pairs treated for HIV, serum concentrations of lamivudine in breastfed infants of mothers treated for HIV are very low (< 4% of maternal serum concentrations) and

progressively decrease to undetectable levels when breastfed infants reach 24 weeks of age. There are no data available on the safety of abacavir and lamivudine when administered to babies less than three months old.

After administration of a single dose of 200 mg zidovudine to HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum.

It is recommended that mothers infected by HIV do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Fertility

Studies in animals showed that neither abacavir nor lamivudine nor zidovudine had any effect on fertility (see section 5.3). Zidovudine has been shown not to affect the number of sperm, sperm morphology and motility in man.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The clinical status of the patient and the adverse event profile of Trizivir should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions have been reported with abacavir, lamivudine and zidovudine used separately or in combination for therapy of HIV disease. Because Trizivir contains abacavir, lamivudine and zidovudine, the adverse reactions associated with these compounds may be expected.

Tabulated list of adverse reactions reported with the individual substances

The adverse reactions reported with abacavir, lamivudine and zidovudine are presented in Table 2. They are listed by body system, organ class and absolute frequency. Frequencies are defined as very common (> 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to < 1/100), rare (> 1/10,000 to < 1/1000), very rare (< 1/10,000). Care must be taken to eliminate the possibility of a hypersensitivity reaction if any of these symptoms occur.

Table 1: Adverse reactions reported with the individual components of Trizivir

Abacavir	Lamivudine	Zidovudine
IMPORTANT: for information on abacavir hypersensitivity see the information below, under the Description of selected adverse reactions **Abacavir hypersensitivity**		
Blood and lymphatic system disorders		
	Uncommon: neutropenia, anaemia (both occasionally severe), thrombocytopenia *Very rare:* pure red cell aplasia	*Common:* anaemia, neutropenia and leucopenia *Uncommon:* thrombocytopenia and pancytopenia with marrow hypoplasia *Rare:* pure red cell aplasia *Very rare:* aplastic anaemia
Immune system disorders		
Common: hypersensitivity		
Metabolism and nutrition disorders		
Common: anorexia		*Rare:* anorexia, lactic acidosis in the absence of hypoxaemia
Psychiatric disorders		
		Rare: anxiety, depression
Nervous system disorders		
Common: headache	*Common:* headache, insomnia *Very rare:* peripheral neuropathy (paraesthesiae)	*Very common:* headache *Common:* dizziness *Rare:* insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions
Cardiac disorders		
		Rare: cardiomyopathy
Respiratory, thoracic and mediastinal disorders		
	Common: cough, nasal symptoms	*Uncommon:* dyspnoea *Rare:* cough

Abacavir	Lamivudine	Zidovudine
Gastrointestinal disorders		
Common: nausea, vomiting, diarrhoea *Rare:* pancreatitis	*Common:* nausea, vomiting, abdominal pain, diarrhoea *Rare:* rises in serum amylase, pancreatitis	*Very common:* Nausea *Common:* vomiting, abdominal pain, and diarrhoea *Uncommon:* flatulence *Rare:* oral mucosa pigmentation, taste disturbance dyspepsia, pancreatitis
Hepatobiliary disorders		
	Uncommon: transient rises in liver enzymes (AST, ALT) *Rare:* hepatitis	*Common:* raised blood levels of liver enzymes and bilirubin *Rare:* liver disorders such as severe hepatomegaly with steatosis,
Skin and subcutaneous tissue disorders		
Common: rash (without systemic symptoms) *Very rare:* erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	*Common:* rash, alopecia	*Uncommon:* rash and pruritus *Rare:* nail and skin pigmentation, urticaria and sweating
Musculoskeletal and connective tissue disorders		
	Common: arthralgia, muscle disorders *Rare:* rhabdomyolysis	*Common:* myalgia *Uncommon:* myopathy
Renal and urinary disorders		
		Rare: urinary frequency
Reproductive system and breast disorders		
		Rare: gynaecomastia
General disorders and administration site conditions		
Common: fever, lethargy, fatigue	*Common:* fatigue, malaise, fever	*Common:* malaise *Uncommon:* fever, generalised pain and asthenia *Rare:* chills, chest pain, and influenza-like syndrome

Many of the adverse reactions listed in the table 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 (see section 4.4). Very rarely cases of erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis

have been reported where abacavir hypersensitivity could not be ruled out. In such cases medicinal products containing abacavir should be permanently discontinued.

Description of selected adverse reactions

Abacavir hypersensitivity
The signs and symptoms of this HSR 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, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry	**Headache**, paraesthesia
Haematological	Lymphopenia
Liver/pancreas	**Elevated liver function tests,** hepatitis, hepatic failure
Musculoskeletal	**Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology	Elevated creatinine, renal failure

Symptoms related to this HSR worsen with continued therapy and can be life- threatening and in rare instance, have been fatal.

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. Similar 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).

Haematological adverse reactions with zidovudine

Anaemia, neutropenia and leucopenia occurred more frequently at higher doses (1,200-1,500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment) and particularly in patients with CD4 cell counts less than 100/mm^3. Dose reduction or cessation of therapy may become necessary (see section 4.4). The anaemia may necessitate transfusions.

The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels were low at the start of zidovudine therapy.

Lactic acidosis

Treatment with nucleoside analogues has been associated with cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, (see section 4.4).

Lipodystrophy

Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Metabolic abnormalities
CART Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience of overdose with Trizivir. No specific symptoms or signs have been identified following acute overdose with zidovudine or lamivudine apart from those listed as adverse reactions. No fatalities occurred, and all patients recovered. Single doses up to 1,200 mg and daily doses up to 1,800 mg of abacavir have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known.

If overdose occurs the patient should be monitored for evidence of toxicity (see section 4.8), 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. Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine, but enhance the elimination of the glucuronide metabolite. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Antivirals for systemic use, antivirals for treatment of HIV infections, combinations. ATC Code: J05AR04.

Mechanism of action
Abacavir, lamivudine and zidovudine are all NRTIs, and are potent selective inhibitors of HIV-1 and HIV-2.All three medicinal products are metabolised sequentially by intracellular kinases to the respective 5′-triphosphate (TP). Lamivudine-TP, carbovir-TP (the active triphosphate form of abacavir) and zidovudine-TP 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, lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases.

No antagonistic effects in vitro were seen with lamivudine and other antiretrovirals (tested agents: abacavir, didanosine and nevirapine). No antagonistic effects in vitro were seen with zidovudine and other antiretrovirals (tested agents: didanosine and interferon-alpha). The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, stavudine or tenofovir, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

In vitro resistance
HIV-1 resistance to lamivudine involves the development of a M184I or, more commonly, M184V amino acid change close to the active site of the viral RT.

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,* requiring multiple mutations for a clinically relevant increase in EC_{50} over wild-type virus.

In vivo resistance (therapy naïve patients)
The M184V or M184I variants arise in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. Most patients experiencing virological failure with a regimen containing abacavir in a pivotal clinical trial with Combivir (fixed dose combination of lamivudine and zidovudine) showed either no NRTI-related changes from baseline (15 %) or only M184V or M184I selection (78 %). The overall selection frequency for M184V or M184I was high (85 %), and selection of L74V, K65R and Y115F was not observed (see Table). Thymidine analogue mutations (TAMs) which are selected by zidovudine (ZDV) were also found (8%).

Therapy	Abacavir + Combivir
Number of Subjects	282
Number of Virological Failures	43
Number of On-Therapy Genotypes	40 (100 %)
K65R	0
L74V	0
Y115F	0
M184V/I	34 (85 %)
TAMs[1]	3 (8 %)

1. Number of subjects with ≥1 TAM.

TAMs might be selected when thymidine analogs are associated with abacavir. In a meta-analysis of six clinical trials, TAMs were not selected by regimens containing abacavir without zidovudine (0/127), but were selected by regimens containing abacavir and the thymidine analogue zidovudine (22/86, 26 %). In addition, the selection of L74V and K65R was reduced when co-administered with ZDV (K65R: without ZDV: 13/127, 10 %; with ZDV: 1/86, 1 %; L74V: without ZDV: 51/127, 40 %; with ZDV: 2/86, 2 %).

In vivo resistance (Therapy experienced patients)
The M184V or M184I variants arise in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy and confers high-level resistance to lamivudine. *In vitro* data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, the available clinical data are very limited and preclude any reliable conclusion in the field. In any case, initiation of susceptible NRTIs should always be preferred to maintenance of lamivudine therapy. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should only be considered in cases where no other active NRTIs are available. Similarly, the presence of TAMs gives rise to resistance to ZDV.

Clinically significant reduction of 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. In a meta-analysis of five clinical trials where abacavir was added to intensify therapy, of 166 subjects, 123 (74 %) had M184V/I, 50 (30 %) had T215Y/F, 45 (27%) had M41L, 30 (18 %) had K70R and 25 (15%) had D67N. K65R was absent and L74V and Y115F were uncommon (≤3 %). Logistic regression modelling of the predictive value for genotype (adjusted for baseline plasma HIV-1 RNA [vRNA], CD4+ cell count, number and duration of prior antiretroviral therapies) showed that the presence of 3 or more NRTI resistance-associated mutations was associated with reduced response at Week 4 ($p=0.015$) or 4 or more mutations at median Week 24 ($p\leq0.012$). In addition, the 69 insertion complex or the Q151M mutation, usually found in combination with A62V, V75I, F77L and F116Y, cause a high level of resistance to abacavir.

Baseline Reverse Transcriptase Mutation	Week 4 (n = 166)		
	n	Median Change vRNA (log_{10} c/mL)	Percent with <400 copies/mL vRNA
None	15	-0.96	40 %
M184V alone	75	-0.74	64 %
Any one NRTI mutation	82	-0.72	65 %
Any two NRTI-associated mutations	22	-0.82	32 %
Any three NRTI-associated mutations	19	-0.30	5 %
Four or more NRTI-associated mutations	28	-0.07	11 %

Phenotypic resistance and cross-resistance
Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple TAMs. Phenotypic cross-resistance to other NRTIs with M184V or M184I mutation alone is limited. Zidovudine, didanosine, stavudine and tenofovir maintain their antiretroviral activities against such HIV-1 variants. The presence of M184V with K65R does give rise to cross-resistance between abacavir, tenofovir, didanosine and lamivudine, and M184V with L74V gives rise to cross-resistance between abacavir, didanosine and lamivudine. The presence of M184V with Y115F gives rise to cross-resistance between abacavir and lamivudine. Appropriate use of abacavir can be guided using currently recommended resistance algorithms.

Cross-resistance between abacavir, lamivudine or zidovudine and antiretrovirals from other classes e.g. PIs or NNRTIs is unlikely.

Clinical efficacy and safety

One randomised, double blind, placebo controlled clinical study has compared the combination of abacavir, lamivudine and zidovudine to the combination of indinavir, lamivudine and zidovudine in treatment naive patients. Due to the high proportion of premature discontinuation (42 % of patients discontinued randomised treatment by week 48), no definitive conclusion can be drawn regarding the equivalence between the treatment regimens at week 48. Although a similar antiviral effect was observed between the abacavir and indinavir containing regimens in terms of proportion of patients with undetectable viral load (≤ 400 copies/ml; intention to treat analysis (ITT), 47 % versus 49 %; as treated analysis (AT), 86 % versus 94 % for abacavir and indinavir combinations respectively), results favoured the indinavir combination, particularly in the subset of patients with high viral load (> 100,000 copies/ml at baseline; ITT, 46 % versus 55 %; AT, 84 % versus 93 % for abacavir and indinavir respectively).

ACTG5095 was a randomised (1:1:1), double-blind, placebo-controlled trial performed in 1147 antiretroviral naïve HIV-1 infected adults, comparing 3 regimens: zidovudine (ZDV), lamivudine (3TC), abacavir (ABC), efavirenz (EFV) vs ZDV/3TC/EFV vs ZDV/3TC/ABC. After a median follow-up of 32 weeks, the tritherapy with the three nucleosides ZDV/3TC/ABC was shown to be virologically inferior to the two other arms regardless of baseline viral load (< or > 100 000 copies/ml) with 26 % of subjects on the ZDV/3TC/ABC arm, 16 % on the ZDV/3TC/EFV arm and 13 % on the 4 drug arm categorised as having virological failure (HIV RNA >200 copies/ml). At week 48 the proportion of subjects with HIV RNA <50 copies/ml were 63 %, 80 % and 86 % for the ZDV/3TC/ABC, ZDV/3TC/EFV and ZDV/3TC/ABC/EFV arms, respectively. The study Data Safety Monitoring Board stopped the ZDV/3TC/ABC arm at this time based on the higher proportion of patients with virologic failure. The remaining arms were continued in a blinded fashion. After a median follow-up of 144 weeks, 25 % of subjects on the ZDV/3TC/ABC/EFV arm and 26 % on the ZDV/3TC/EFV arm were categorised as having virological failure. There was no significant

difference in the time to first virologic failure (p=0.73, log-rank test) between the 2 arms. In this study, addition of ABC to ZDV/3TC/EFV did not significantly improve efficacy.

		ZDV/3TC/ABC	ZDV/3TC/EFV	ZDV/3TC/ABC/EFV
Virologic failure (HIV RNA >200 copies/ml)	32 weeks	26 %	16 %	13 %
	144 weeks	-	26 %	25 %
Virologic success (48 weeks HIV RNA < 50 copies/ml)		63 %	80 %	86 %

In antiretroviral-naive patients treated with a combination of abacavir, lamivudine, zidovudine and efavirenz in a small, ongoing, open label pilot study, the proportion of patients with undetectable viral load (< 400 copies/ml) was approximately 90 % with 80 % having < 50 copies/ml after 24 weeks of treatment.

Currently there are no data on the use of Trizivir in heavily pre-treated patients, patients failing on other therapies or patients with advanced disease (CD4 cells < 50 cells/mm^3).

The degree of benefit of this nucleoside combination in heavily pre-treated patients will depend on the nature and duration of prior therapy that may have selected for HIV-1 variants with cross-resistance to abacavir, lamivudine or zidovudine.

To date there are insufficient data on the efficacy and safety of Trizivir given concomitantly with NNRTIs or PIs.

5.2 Pharmacokinetic properties

Absorption

Abacavir, lamivudine and zidovudine are rapidly and well absorbed from the gastro-intestinal tract following oral administration. The absolute bioavailability of oral abacavir, lamivudine and zidovudine in adults is about 83 %, 80 - 85 % and 60 - 70 % respectively.

In a pharmacokinetic study in HIV-1 infected patients, the steady state pharmacokinetic parameters of abacavir, lamivudine and zidovudine were similar when either Trizivir alone or the combination tablet lamivudine/zidovudine and abacavir in combination were administered, and also similar to the values obtained in the bioequivalence study of Trizivir in healthy volunteers.

A bioequivalence study compared Trizivir with abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg taken together. The effect of food on the rate and extent of absorption was also studied. Trizivir was shown to be bioequivalent to abacavir 300 mg, lamivudine 150 mg and zidovudine 300 mg given as separate tablets for $AUC_{0-\infty}$ and C_{max}. Food decreased the rate of absorption of Trizivir (slight decrease C_{max} (mean 18 - 32 %) and increase t_{max} (approximately 1 hour), but not the extent of absorption ($AUC_{0-\infty}$). These changes are not considered clinically relevant and no food restrictions are recommended for administration of Trizivir.

At a therapeutic dose (one Trizivir tablet twice daily) in patients, the mean (CV) steady-state C_{max} of abacavir, lamivudine and zidovudine in plasma are 3.49 µg/ml (45 %), 1.33 µg/ml (33 %) and 1.56 µg/ml (83 %), respectively. Corresponding values for C_{min} could not be established for abacavir and are 0.14 µg/ml (70 %) for lamivudine and 0.01 µg/ml (64 %) for zidovudine. The mean (CV) AUCs for abacavir, lamivudine and zidovudine over a dosing interval of 12 hours are 6.39 µg.h/ml (31 %), 5.73 µg.h/ml (31 %) and 1.50 µg.h/ml (47 %), respectively.

A modest increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) was not significantly altered. Zidovudine has no effect on the

pharmacokinetics of lamivudine. An effect of abacavir is observed on zidovudine (C_{max} reduced with 20 %) and on lamivudine (C_{max} reduced with 35 %).

Distribution

Intravenous studies with abacavir, lamivudine and zidovudine showed that the mean apparent volume of distribution is 0.8, 1.3 and 1.6 l/kg respectively. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 36 % serum albumin *in vitro*). Zidovudine plasma protein binding is 34 % to 38 %. Plasma protein binding studies *in vitro* indicate that abacavir binds only low to moderately (~ 49 %) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for interactions with other medicinal products through plasma protein binding displacement.

Interactions involving binding site displacement are not anticipated with Trizivir.

Data show that abacavir, lamivudine and zidovudine penetrate the central nervous system (CNS) and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum lamivudine and zidovudine concentrations 2 - 4 hours after oral administration were approximately 0.12 and 0.5 respectively. The true extent of CNS penetration of lamivudine and its relationship with any clinical efficacy is unknown.

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**.**

Biotransformation

Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of unchanged lamivudine. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism (5 - 10 %) and low plasma binding.

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50 - 80 % of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

Abacavir is primarily metabolised by the liver with approximately 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 dose excreted in the urine.

Elimination

The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70 %) via the organic cationic transport system. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. Dose reduction is required for patients with creatinine clearance ≤ 50 ml/min (see section 4.2).

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 l/h/kg. Renal clearance of zidovudine is estimated to be 0.34 l/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

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.

Special patient populations

Hepatic impairment

There are no data available on the use of Trizivir in hepatically impaired patients. Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Data obtained in patients with moderate to severe hepatic impairment show that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction.

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) receiving a single 600 mg dose. The results showed that there was a mean increase of 1.89 fold [1.32; 2.70] in the abacavir AUC, and 1.58 [1.22; 2.04] fold in the elimination half-life. No recommendation on dose reduction is possible in patients with mild hepatic impairment due to substantial variability of abacavir exposure in this patient population. 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 (see section 4.3).

Renal impairment

The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70 %) via the organic cationic transport system. Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction.

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6 l/h/kg. Renal clearance of zidovudine is estimated to be 0.34 l/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine concentrations are increased in patients with advanced renal failure.

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, and, therefore, no dose reduction is required in patients with renal impairment.

As dose adjustments of lamivudine and zidovudine may be necessary it is recommended that separate preparations of abacavir, lamivudine and zidovudine be administered to patients with reduced renal function (creatinine clearance ≤ 50 ml/min). Trizivir is contraindicated in patients with end-stage renal disease (see section 4.3).

Elderly

No pharmacokinetic data are available in patients over 65 years of age.

5.3 Preclinical safety data

There are no data available on treatment with the combination of abacavir, lamivudine and zidovudine in animals. The clinically relevant toxicological effects of these three medicinal products are anaemia, neutropenia and leucopenia.

Mutagenicity and carcinogenicity

Neither abacavir, lamivudine nor zidovudine is mutagenic in bacterial tests, but consistent with other nucleoside analogues, they inhibit cellular DNA replication in *in vitro* mammalian tests such as the mouse lymphoma assay.

Lamivudine has not shown any genotoxic activity in the *in vivo* studies at doses that gave plasma concentrations up to 40 - 50 times higher than clinical plasma levels. Zidovudine showed clastogenic effects in oral repeated dose micronucleus tests in mice and rats. Peripheral blood lymphocytes from AIDS patients receiving zidovudine treatment have also been observed to contain higher numbers of chromosome breakages.

A pilot study has demonstrated that zidovudine is incorporated into leukocyte nuclear DNA of adults, including pregnant women, taking zidovudine as treatment for HIV-1 infection, or for the prevention of mother to child viral transmission. Zidovudine was also incorporated into DNA from cord blood leukocytes of infants from zidovudine-treated mothers. A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

Abacavir has a weak potential to cause chromosomal damage both *in vitro* and *in vivo* at high test concentrations and therefore any potential risk to man must be balanced against the expected benefits of treatment.

The carcinogenic potential of a combination of abacavir, lamivudine and zidovudine has not been tested. In long-term oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. In oral carcinogenicity studies with zidovudine in mice and rats, late appearing vaginal epithelial tumours were observed. A subsequent intravaginal carcinogenicity study confirmed the hypothesis that the vaginal tumours were the result of long term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine. There were no other zidovudine-related tumours observed in either sex of either species.

In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study, by the US National Cancer Institute, zidovudine was administered at maximum tolerated doses to pregnant mice from day 12 to 18 of gestation. One year postnatally, there was an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months, with exposure beginning prenatally on gestation day 10. Treatment related findings were limited to late-occurring vaginal epithelial tumours, which were seen with a similar incidence and time of onset as in the standard oral carcinogenicity study. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.

It is concluded that as the increase in incidence of tumours in the first transplacental carcinogenicity study represents a hypothetical risk, this should be balanced against the proven therapeutic benefit. 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 rats in the thyroid gland of males and and in the liver, urinary bladder, lymph nodes and the subcutis of females.

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. The exception was the preputial gland tumour which occurred at a dose of 110 mg/kg in mice. The systemic exposure at the no effect level in mice and rats was equivalent to 3 and 7 times the human systemic exposure during therapy.

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

Repeat-dose toxicity

In toxicology studies abacavir was shown to increase liver weights in rats and monkeys. The clinical relevance of this is unknown. There is no evidence from clinical studies that abacavir is hepatotoxic. Additionally, autoinduction of abacavir metabolism or induction of the metabolism of other medicinal products hepatically metabolised has not been observed in man.

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

Lamivudine was not teratogenic in animal studies but there were indications of an increase in early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in humans. A similar effect was not seen in rats even at very high systemic exposure.

Zidovudine had a similar effect in both species, but only at very high systemic exposures. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of foetal abnormalities was observed at lower doses.

Abacavir demonstrated toxicity to the developing embryo and foetus in rats, but not in rabbits. These findings included decreased foetal body weight, foetal oedema, and an increase in skeletal variations/malformations, early intra-uterine deaths and still births. No conclusion can be drawn with regard to the teratogenic potential of abacavir because of this embryo-foetal toxicity.

A fertility study in the rat has shown that abacavir had no effect on male or female fertility. Likewise, neither lamivudine nor zidovudine had any effect on fertility. Zidovudine has not been shown to affect the number of sperm, sperm morphology and motility in man.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
microcrystalline cellulose,
sodium starch glycollate (type A),
magnesium stearate.

Tablet Coating:
Opadry Green 03B11434 containing: hypromellose, titanium dioxide, polyethylene glycol, indigo carmine aluminium lake, iron oxide yellow.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

2 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Trizivir tablets are available in opaque white PCTFE/PVC-Al blister packs or child-resistant foil PVC/PCTFE/PVC-Al/Paper blister packs containing 60 tablets, or child resistant HDPE bottles containing 60 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/156/002 – opaque white PCTFE/PVC-Al Blister pack (60 Tablets)
EU/1/00/156/003 -Bottle pack (60 Tablets)
EU/1/00/156/004 - child-resistant foil PVC/PCTFE/PVC-Al/Paper Blister pack (60 Tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 January 2001

Date of latest renewal: 2 January 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S)RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations),
Priory Street,
Ware,
Hertfordshire, SG 12 0DJ, UK

Or

GlaxoSmithKline Pharmaceuticals S.A.
ul. Grunwaldzka 189
60-322 Poznan
Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal

D. CONDITIONS OR RESTRICTIONSWITH REGARD TO THE SAFE ANDEFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time

- **Additional risk minimisation measures**

The EU RMP of the abacavir (ABC) containing products (Ziagen, Kivexa and Trizivir) includes the following risk minimisation plan in relation to abacavir hypersensitivitiy reaction (HSR), which is an important identified risk:

Safety Concern	**ABC Hypersensitivity (including risk of reduced clinical vigilance for ABC HSR following HLA-B*5701 screening).**
Routine risk minimisation activities	The EU SPC provides detailed information and advice relating to ABC HSR
Additional risk minimisation activity	**Objective and rationale:** Increased understanding and awareness of ABC HSR.
	Proposed actions: Provision of updated ABC HSR education materials for healthcare professionals to countries where the MAH has marketing authorisation for ABC.
	Criteria to be used to verify the success of proposed risk minimisation activity: Implementation of the education program will be monitored by the MAH via auditing.
	Proposed review period: Materials will be reviewed annually.

ABC HSR Education Programme has been in place since the first approval of ABC as the single active preparation, ZIAGEN (USA December 1998, EU July 1999).

Key elements included in the educational material to increase understanding and awareness of ABC HSR and expand on the information already included in the currently approved EU SPC:

1. **Major symptoms associated with ABC HSR** are fever (~80%), rash (~70%), gastrointestinal symptoms (>50%) such as nausea, abdominal pain, vomiting, and diarrhoea, generalise malaise, fatigue, and headache (~50%) and other symptoms (~30%) such as respiratory, mucosal, and musculoskeletal symptoms.

Based on the above patients are advised to contact their physician immediately to determine whether they should stop taking abacavir if:

- presence of skin rash; OR
- development of 1 or more symptom from at least 2 of the following groups:
  - Fever
  - Shortness of breath, sore throat or cough
  - Nausea or vomiting or diarrhoea or abdominal pain
  - Extreme tiredness or achiness or generally ill feeling

2. **Risk factors for ABC HSR**

HLA-B*5701 is the only identified pharmacogenetic marker that is consistently associated with clinical diagnosis of an ABC HSR reaction. However, some patients with a suspected ABC hypersensitivity reaction may not have the HLA-B*5701 allele.

3. **Recommendations for HLA-B*5701 screening**

In settings where validated screening methods are available, clinicians should consider screening for HLA-B*5701 in any HIV-infected patient who has not previously been exposed to ABC. Clinical diagnosis of suspected hypersensitivity to ABC remains the basis for clinical decision making. HLA-B*5701 screening for risk of ABC hypersensitivity should never be substituted for appropriate clinical vigilance and patient management in individuals receiving ABC. If ABC hypersensitivity cannot be ruled out, ABC should be permanently discontinued, regardless of the results of HLA-B*5701 screening.

4. Information on HLA-B*5701 testing

The one-time HLA-B*5701 test identifies people at high risk for this serious allergic reaction. The gold standards for HLA-B*5701 screening are sequence-based genotyping and polymerase chain reaction sequencing of specific oligonucleotide probes. Blood or saliva samples are collected and tested for genetic sequences coding for the HLA-B*5701 allele. Results of PREDICT-1 and SHAPE studies show that the presence of the HLA-B*5701 allele is associated with increased risk of ABC hypersensitivity, regardless of race, screening for HLA-B*5701 before starting treatment with ABC may identify subjects at increased risk of a HSR, avoiding treatment with ABC in subjects with the HLA-B*5701 allele was shown to significantly reduce the incidence rate of clinically diagnosed cases of hypersensitivity. Data from these studies do not support the use of skin patch testing in routine clinical practice. Only patients found to lack the HLA-B*5701 allele should begin therapy with ABC.

5. Management of ABC HSR reaction

Symptoms can occur at any time during treatment with ABC, but usually occur within the first 6 weeks of therapy. Symptoms are initially mild and evolve over days, becoming more severe with continued ABC therapy. Symptoms improve on cessation of ABC. Rechallenge can result in a more rapid and severe reaction, which can be fatal, therefore rechallenge is contraindicated.

6. Hypersensitivity case studies

The educational material includes 3 case studies to demonstrate different clinical scenarios and their management.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON x 60 FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Trizivir 300 mg/150 mg/300 mg film-coated tablets
abacavir/lamivudine/zidovudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains:
abacavir 300 mg (as sulfate)
lamivudine 150 mg
zidovudine 300 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Detach enclosed Alert Card, it contains important safety information

WARNING! In case of any symptoms suggesting hypersensitivity reactions, contact your doctor IMMEDIATELY.

"**Pull here**" (with Alert card attached)

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/156/002 PCTFE/PVC-Al
EU/1/00/156/004 PVC/PCTFE/PVC-Al/Paper

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trizivir

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER x 60 FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Trizivir 300 mg/150 mg/300 mg tablets
abacavir/lamivudine/zidovudine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE CARTON x 60 FILM COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Trizivir 300 mg/150 mg/300 mg film-coated tablets
abacavir/lamivudine/zidovudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains:
abacavir 300 mg (as sulfate)
lamivudine 150 mg
zidovudine 300 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Detach enclosed Alert Card, it contains important safety information

WARNING! In case of any symptoms suggesting hypersensitivity reactions, contact your doctor IMMEDIATELY.

"**Pull here**" (with Alert card attached)

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/156/003

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

trizivir

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL x 60 FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Trizivir 300 mg/150 mg/300 mg film-coated tablets
abacavir/lamivudine/zidovudine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains:
abacavir 300 mg (as sulfate)
lamivudine 150 mg
zidovudine 300 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACHOF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/156/003

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

TRIZIVIR TABLETS ALERT CARD (blister and bottle pack)

SIDE 1

IMPORTANT - ALERT CARD
TRIZIVIR (abacavir sulfate / lamivudine / zidovudine) Tablets
Carry this card with you at all times

Since Trizivir contains abacavir some patients taking Trizivir may develop a hypersensitivity reaction (serious allergic reaction) which **can be life-threatening** if treatment with Trizivir is continued.
CONTACT YOUR DOCTOR IMMEDIATELY for advice on whether you should stop taking Trizivir if:

1) you get a skin rash OR
2) you get one or more symptoms from at least TWO of the following groups

- fever
- shortness of breath, sore throat or cough
- nausea or vomiting or diarrhoea or abdominal pain
- severe tiredness or achiness or generally feeling ill

If you have discontinued Trizivir due to this reaction, **YOU MUST NEVER TAKE** Trizivir, or any medicine containing abacavir (**Kivexa**, **Ziagen or Triumeq**) again as **within hours** you may experience a life-threatening lowering of your blood pressure or death.

(see reverse of card)

SIDE 2

You should immediately contact your doctor if you think you are having a hypersensitivity reaction to Trizivir. Write your doctor's details below:

Doctor:.....……

Tel:.....……

If your doctor is not available, you must urgently seek alternative medical advice (e.g. the emergency unit of the nearest hospital).

For general Trizivir information enquiries, contact (local company name and telephone number inserted here)

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Trizivir 300 mg/150 mg/300 mg film-coated tablets
abacavir/lamivudine/zidovudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- **If you get any side effects talk to your doctor or pharmacist immediately**. **This includes any possible side effects not listed in this leaflet.** See section 4.

IMPORTANT — Hypersensitivity reactions

Trizivir contains abacavir (which is also an active substance in medicines such as **Kivexa, Triumeq** and **Ziagen**). Some people who take abacavir may develop a **hypersensitivity reaction** (a serious allergic reaction), which can be life-threatening if they continue to take abacavir containing products . **You must carefully read all the information under 'Hypersensitivity reactions' in the panel in Section 4**.

The Trizivir pack includes an **Alert Card**, to remind you and medical staff about abacavir hypersensitivity. **Detach this card and keep it with you at all times**.

What is in this leaflet

1. What Trizivir is and what it is used for

Trizivir is used to treat HIV (human immunodeficiency virus) infection in adults.

Trizivir contains three active ingredients that are used to treat HIV infection: abacavir, lamivudine and zidovudine. All of these belong to a group of anti-retroviral medicines called *nucleoside analogue reverse transcriptase inhibitors (NRTIs)*.

Trizivir helps to control your condition. Trizivir does not cure HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. This helps your body to increase the CD4 cell count in your blood. CD4 cells are a type of white blood cell that are important in helping your body to fight infection.

Not everyone responds to treatment with Trizivir in the same way. Your doctor will monitor the effectiveness of your treatment.

2. What you need to know before you take Trizivir

Do not take Trizivir:

- if you are **allergic** *(hypersensitive)* to abacavir (or any other medicine containing abacavir — **Kivexa, Triumeq** or **Ziagen**), lamivudine or zidovudine, or any of the other ingredients of this medicine *(listed in Section 6)*
  Carefully read all the information about hypersensitivity reactions in Section 4.
- if you have **liver problems**
- if you have **severe kidney problems**
- if you have **a very low red blood cell count** *(anaemia)* or **a very low white blood cell count** *(neutropenia)*
  Check with your doctor if you think any of these apply to you.

Take special care with Trizivir

Some people taking Trizivir are more at risk of serious side effects. You need to be aware of the extra risks:

- if you have ever had **liver disease,** including hepatitis B or C (if you have hepatitis B infection, do not stop Trizivir without your doctor's advice, as your hepatitis may come back)
- if you are seriously **overweight** (especially if you are a woman)
- if you are **diabetic** using insulin
  Talk to your doctor if any of these apply to you before using Trizivir You may need extra check-ups, including blood tests, while you are taking your medicine. **See Section 4 for more information**.

Abacavir hypersensitivity reactions
Even patients who don't have the HLA-B*5701 gene may still develop a **hypersensitivity reaction** (a serious allergic reaction).

Carefully read all the information about hypersensitivity reactions in Section 4 of this leaflet.

Risk of heart attack
It cannot be excluded that abacavir may increase the risk of having a heart attack.
Tell your doctor if you have heart problems, if you smoke, or have other illnesses that may increase your risk of heart disease such as high blood pressure, or diabetes. Do not stop taking Trizivir unless your doctor advises you to do so.

Look out for important symptoms
Some people taking Trizivir develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking Trizivir.
Read the information 'Other possible side effects of Trizivir' in Section 4 of this leaflet.

Protect other people
HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

Other medicines and Trizivir
Tell your doctor or pharmacist if you are taking any other medicines, or if you have taken any recently, including herbal medicines or other medicines you bought without a prescription.

Remember to tell your doctor or pharmacist if you begin taking a new medicine while you are taking Trizivir.

These medicines should not be used with Trizivir:
- stavudine or emtricitabine, to treat **HIV infection**
- other medicinal products containing lamivudine, used to treat **HIV infection** or **hepatitis B infection**
- ribavirin or injections of ganciclovir to treat **viral infections**
- high doses of **co-trimoxazole**, an antibiotic
- cladribine, used to treat **hairy cell leukaemia**

Tell your doctor if you are being treated with any of these.

Some medicines can make it more likely that you will have side effects, or make side effects worse

These include:
- sodium valproate, to treat **epilepsy**
- interferon, to treat **viral infections**
- pyrimethamine, to treat **malaria** and other parasitic infections
- dapsone, to prevent **pneumonia** and treat skin infections
- fluconazole or flucytosine, to treat **fungal infections** such as **candida**
- pentamidine or atovaquone, to treat parasitic infections such as **PCP**
- amphotericin or co-trimoxazole, to treat **fungal and bacterial infections**
- probenecid, to treat **gout** and similar conditions, and given with some antibiotics to make them more effective
- **methadone**, used as a **heroin substitute**
- vincristine, vinblastine or doxorubicin, to treat **cancer**

Tell your doctor if you're taking any of these.

Some medicines interact with Trizivir
These include:
- **clarithromycin**, an antibiotic

  If you are taking clarithromycin, take your dose at least 2 hours before or after you take your Trizivir.
- **phenytoin**, for treating **epilepsy**

  Tell your doctor if you are taking phenytoin. Your doctor may need to monitor you while you are taking Trizivir.

Methadone and Trizivir
Abacavir increases the rate at which methadone is removed from the body. If you are taking methadone, you will be checked for any withdrawal symptoms. Your methadone dose may need to be changed.

Pregnancy
If you are pregnant, if you become pregnant or if you are planning to become pregnant, talk to your doctor about the risks and benefits to you and your baby of taking Trizivir during your pregnancy.

Trizivir and similar medicines may cause side effects in unborn babies. If you become pregnant while you are taking Trizivir, your baby may be given extra check-ups (including blood tests) to make sure it is developing normally.

Children whose mothers took NRTIs (medicines like Trizivir) during pregnancy have a reduced risk of being infected with HIV. This benefit is greater than the risk of having side effects.

Breast-feeding
Women who are HIV-positive must not breast-feed, because HIV infection can be passed on to the baby in breast milk. A small amount of the ingredients in Trizivir can also pass into your breast milk. If you are breast-feeding, or thinking about breast-feeding:

Talk to your doctor immediately.

Driving and using machines
Trizivir can make you dizzy and have other side effects that make you less alert.
Don't drive or operate machines unless you're feeling well.

3. How to take Trizivir

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Keep in touch with your doctor, and do not stop taking Trizivir without your doctor's advice.

How much to take
The usual dose of Trizivir for adults is one tablet twice a day.

Take the tablets at regular times, leaving approximately 12 hours between each tablet.

Swallow the tablets whole, with some water. Trizivir can be taken with or without food.

If you take more Trizivir than you should
If you accidentally take too much Trizivir, tell your doctor or your pharmacist, or contact your nearest hospital emergency department for further advice.

If you forget to take Trizivir
If you forget to take a dose, take it as soon as you remember. Then continue your treatment as before. Do not take a double dose to make up for a forgotten dose.

It is important to take Trizivir regularly, because if you take it at irregular intervals it may not continue to work against the HIV infection, and you may be more likely to have a hypersensitivity reaction.

If you have stopped taking Trizivir
If you have stopped taking Trizivir for any reason — especially because you think you are having side effects, or because you have other illness:

Talk to your doctor before you start taking it again. Your doctor will check whether your symptoms were related to a hypersensitivity reaction. If the doctor thinks they may have been related, **you will be told never again to take Trizivir, or any other medicine containing abacavir (Kivexa or Ziagen)**. It is important that you follow this advice.

If your doctor advises that you can start taking Trizivir again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everyone gets them.

When you are being treated for HIV, it can be hard to tell whether a symptom is a side effect of Trizivir or other medicines you are taking, or an effect of the HIV infection itself. **So it is very important to talk to your doctor about any changes in your health**.

Even patients who don't have the HLA-B*5701 gene may still develop **a hypersensitivity reaction** (a serious allergic reaction), described in this leaflet in the panel headed 'Hypersensitivity reactions'.

It is very important that you read and understand the information about this serious reaction.

As well as the side effects listed below for Trizivir, other conditions can develop during treatment. It is important to read the information on the other side of this leaflet under 'Other possible side effects of Trizivir'.

Hypersensitivity reactions

Trizivir contains **abacavir** (which is also an active substance in **Kivexa, Triumeq** and **Ziagen**). Abacivir can cause a serious allergic reaction known as a hypersensitivity reaction. These hypersensitivity reactions have been seen more frequently in people taking medicines that contain abacavir.

Who gets these reactions?

Anyone taking Trizivir could develop a hypersensitivity reaction to abacavir, which could be life threatening if they continue to take Trizivir.

You are more likely to develop such a reaction if you have a gene called **HLA-B*5701** (but you can get a reaction even if you do not have this gene). You should have been tested for this gene before Trizivir was prescribed for you. **If you know you have this gene, tell your doctor before you take Trizivir.**

About 3 to 4 in every 100 patients treated with abacavir in a clinical trial who did not have the HLA-B*5701 gene developed a hypersensitivity reaction.

What are the symptoms?

The most common symptoms are:

- **fever** (high temperature) and **skin rash**

Other common symptoms are:

- nausea (feeling sick), vomiting (being sick), diarrhoea, abdominal (stomach) pain, severe tiredness

Other symptoms include:

Pains in the joints or muscles, swelling of the neck, shortness of breath, sore throat, cough, occasional headaches, inflammation of the eye (conjunctivitis), mouth ulcers, low blood pressure, tingling or numbness of the hands or feet.

If you continue to take Trizivir, the symptoms will get worse, and may be life-threatening.

When do these reactions happen?

Hypersensitivity reactions can start at any time during treatment with Trizivir, but are more likely during the first 6 weeks of treatment.

Contact your doctor immediately:

1 if you get a skin rash, OR

2 if you get symptoms from at least 2 of the following groups:

- fever
- shortness of breath, sore throat or cough
- nausea or vomiting, diarrhoea or abdominal pain
- severe tiredness or achiness, or generally feeling ill

Your doctor may advise you to stop taking Trizivir.

If you have stopped taking Trizivir

If you have stopped taking Trizivir because of a hypersensitivity reaction, **you must NEVER AGAIN take Trizivir, or any other medicine containing abacavir (Kivexa, Triumeq or Ziagen)**. If you do, within hours, your blood pressure could fall dangerously low, which could result in death.

If you have stopped taking Trizivir for any reason — especially because you think you are having side effects, or because you have other illness:

Talk to your doctor before you start again. Your doctor will check whether your symptoms were related to a hypersensitivity reaction. If the doctor thinks they may have been, **you will then be**

told never again to take Trizivir, or any other medicine containing abacavir (Kivexa, Triumeq or Ziagen). It is important that you follow this advice.

Occasionally, hypersensitivity reactions have developed in people who start taking abacavir containing products again, but who had only one symptom on the Alert Card before they stopped taking it.

Very rarely, patients who have taken medicines containing abacavir in the past without any symptoms of hypersensitivity have developed a hypersensitivity reaction when they start taking these medicines again.

If your doctor advises that you can start taking Trizivir again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it.

If you are hypersensitive to Trizivir, return all your unused Trizivir tablets for safe disposal. Ask your doctor or pharmacist for advice.

The Trizivir pack includes an **Alert Card**, to remind you and medical staff about hypersensitivity reactions. **Detach this card and keep it with you at all times**.

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- feeling sick *(nausea)*

Common side effects
These may affect **up to 1 in 10** people:
- hypersensitivity reaction
- being sick *(vomiting)*
- diarrhoea
- stomach pains
- loss of appetite
- feeling dizzy
- tiredness, lack of energy
- fever (high temperature)
- general feeling of being unwell
- difficulty in sleeping *(insomnia)*
- muscle pain and discomfort
- joint pain
- cough
- irritated or runny nose
- skin rash
- hair loss

Common side effects that may show up in blood tests are:
- a low red blood cell count *(anaemia)* or low white blood cell count *(neutropenia or leucopenia)*
- an increase in the level of liver enzymes
- an increased amount in the blood of *bilirubin* (a substance produced in the liver) which may make your skin appear yellow

Uncommon side effects
These may affect **up to 1 in 100** people:
- feeling breathless
- wind *(flatulence)*
- itching

- muscle weakness

An uncommon side effect that may show up in blood tests is:
- a decrease in the number of cells involved in blood clotting (thrombocytopenia), or in all kinds of blood cells *(pancytopenia)*

Rare side effects
These may affect **up to 1 in 1000** people:
- liver disorders, such as jaundice, enlarged liver or fatty liver, inflammation *(hepatitis)*
- lactic acidosis (*see the next section, 'Other possible side effects of Trizivir'*)
- inflammation of the pancreas *(pancreatitis)*
- chest pain; disease of the heart muscle *(cardiomyopathy)*
- fits (convulsions)
- feeling depressed or anxious, not being able to concentrate, feeling drowsy
- indigestion, taste disturbance
- changes in the colour of your nails, your skin, or the skin inside your mouth
- a flu-like feeling — chills and sweating
- tingly feelings in the skin (pins and needles)
- sensation of weakness in the limbs
- breakdown of muscle tissue
- numbness
- passing urine more often
- enlarged breasts in men

Rare side effects that may show up in blood tests are:
- increase in an enzyme called amylase
- a failure of the bone marrow to produce new red blood cells *(pure red cell aplasia)*

Very rare side effects
These may affect **up to 1 in 10,000** people:
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme)*
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals *(Stevens–Johnson syndrome)*, and a more severe form causing skin peeling in more than 30% of the body surface *(toxic epidermal necrolysis)*

If you notice any of these symptoms contact a doctor urgently.

A very rare side effect that may show up in blood tests is:
- a failure of the bone marrow to produce new red or white blood cells (*aplastic anaemia*)

If you get side effects

Tell your doctor or pharmacist if any of the side effects gets severe or troublesome, or if you notice any side effects not listed in this leaflet.

Other possible side effects of Trizivir

Trizivir may cause other conditions to develop during HIV treatment.

Symptoms of infection and inflammation

Old infections may flare up

People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of inflammation. These symptoms are

probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections. Symptoms usually include **fever**, plus some of the following:

- headache
- stomach ache
- difficulty breathing

In rare cases, as the immune system becomes stronger, it can also attack healthy body tissue (*autoimmune disorders*). The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection. Symptoms may include:

- palpitations (rapid or irregular heartbeat) or tremor
- hyperactivity (excessive restlessness and movement)

weakness beginning in the hands and feet and moving up towards the trunk of the body

If you get any symptoms of infection while you're taking Trizivir:

Tell your doctor immediately. Do not take other medicines for the infection without your doctor's advice.

Your body shape may change

People taking combination therapy for HIV may find that their body shape changes, because of changes in fat distribution:

- Fat may be lost from the legs, arms or face
- Extra fat may build up around the tummy (abdomen), or on the breasts or internal organs
- Fatty lumps (sometimes called buffalo hump) may appear on the back of the neck

It is not yet known what causes these changes, or whether they have any long-term effects on your health. If you notice changes in your body shape:

Tell your doctor.

Lactic acidosis is a rare but serious side effect

Some people taking Trizivir, or other medicines like it (NRTIs), develop a condition called lactic acidosis, together with an enlarged liver.

Lactic acidosis is caused by a build-up of lactic acid in the body. It is rare; if it happens, it usually develops after a few months of treatment. It can be life-threatening, causing failure of internal organs.

Lactic acidosis is more likely to develop in people who have liver disease, or in obese (very overweight) people, especially women.

Signs of lactic acidosis include:

- feeling sick (nausea), being sick (vomiting)
- stomach pain
- generally feeling unwell
- loss of appetite, weight loss
- deep, rapid, difficult breathing
- numbness or weakness in the limbs

During your treatment, your doctor will monitor you for signs of lactic acidosis. If you have any of the symptoms listed above or any other symptoms that worry you:

See your doctor as soon as possible.

You may have problems with your bones

Some people taking combination therapy for HIV develop a condition called osteonecrosis. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids

- if they drink alcohol
- if their immune systems are very weak
- if they are overweight

Signs of osteonecrosis include:
- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving

If you notice any of these symptoms:
Tell your doctor.

Other effects may show up in blood tests

Trizivir can also cause:
- increased levels of lactic acid in the blood, which on rare occasions can lead to lactic acidosis
- increased levels of sugar and fats (triglycerides and cholesterol) in the blood
- resistance to insulin (so if you are diabetic, you may have to change your insulin dose to control your blood sugar)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Trizivir

Keep this medicine out of the sight and reach of children.

Do not take this medicine after the expiry date shown on the carton. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures help protect the environment.

6. Contents of the pack and other information

What Trizivir contains
The active substances in each Trizivir film-coated tablet are 300 mg of abacavir (as sulfate), 150 mg lamivudine and 300 mg zidovudine.

The other ingredients are microcrystalline cellulose, sodium starch glycollate and magnesium stearate in the core of the tablet. The tablet coating contains hypromellose, titanium dioxide, polyethylene glycol, indigo carmine aluminium lake, iron oxide yellow.

What Trizivir looks like and contents of the pack
Trizivir film-coated tablets are engraved with ‘GX LL1’ on one side. They are blue/green and capsule-shaped and are provided in blister packs containing 60 tablets or bottles containing 60 tablets with child-resistant tops.

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Manufacturer
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or

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu