

# DATA SHEET

## TRIZIVIR<sup>®</sup> Tablets

*300mg of Abacavir as Abacavir sulfate, 150mg Lamivudine and 300mg Zidovudine.*

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### Qualitative and quantitative composition

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Each tablet contains 300mg of abacavir as abacavir sulfate, 150mg lamivudine and 300mg zidovudine.

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### Pharmaceutical form

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Film-coated tablets.

The capsule shaped film-coated tablets are blue/green and engraved with GX LL1 on one side.

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### Clinical particulars

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#### ***Therapeutic Indications***

TRIZIVIR is a combination of three nucleoside analogues (abacavir, lamivudine and zidovudine). It is indicated in antiretroviral therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents over the age of 12 years.

#### ***Posology and Method of Administration***

The recommended dose of TRIZIVIR in adults and adolescents over 12 years of age is one tablet twice daily.

TRIZIVIR should not be administered to adolescents and adults who weigh less than 40 kg because it is a fixed-dose tablet, therefore the dose cannot be reduced.

TRIZIVIR can be taken with or without food.

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

Where discontinuation of therapy with one of the active substances of TRIZIVIR is indicated, or where dose reduction is necessary separate

preparations of abacavir (ZIAGEN<sup>®</sup>), lamivudine (3TC<sup>®</sup>) and zidovudine (Retrovir<sup>®</sup>) are available.

*Renal impairment:* Dosage reduction of lamivudine or zidovudine may be necessary in renally impaired patients. It is therefore recommended that separate preparations of abacavir, lamivudine and zidovudine should be administered to patients with reduced renal function (creatinine clearance <50mL/min) (see Pharmacokinetic Properties).

*Hepatic impairment:* TRIZIVIR is contra-indicated for use in hepatically impaired patients (see Contra-indications and Pharmacokinetic Properties).

*Elderly:* No pharmacokinetic data is 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.

*Dosage adjustments in patients with haematological adverse reactions:* Dosage adjustment of zidovudine may be necessary if the haemoglobin level falls below 9g/dL or 5.59mmol/L or the neutrophil count falls below  $1.0 \times 10^9/L$  (see Contraindications and Special Warnings and Special Precautions for Use). Separate preparations of abacavir, zidovudine and lamivudine should therefore be administered to these patients.

### **Contra-indications**

TRIZIVIR is contraindicated in patients with known hypersensitivity to TRIZIVIR or any of its components (abacavir, lamivudine or zidovudine), or to any of the excipients of TRIZIVIR tablets.

TRIZIVIR is contraindicated in patients with hepatic impairment.

Due to the active ingredient zidovudine, TRIZIVIR is contraindicated in patients with abnormally low neutrophil counts ( $<0.75 \times 10^9/L$ ), or abnormally low haemoglobin levels ( $<7.5g/dL$  or  $4.65mmol/L$ ) (see Special Warnings and Special Precautions for Use).

### **Special Warnings and Special Precautions for Use**

#### **Hypersensitivity to abacavir** (see also Undesirable Effects):

In clinical studies, approximately 5% of subjects receiving abacavir developed a hypersensitivity reaction, which in rare cases has proved fatal.

- Risk Factors

Studies have shown that carriage of the HLA-B\*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. In the prospective study CNA106030 (PREDICT-1), use of pre-therapy screening for the HLA-B\*5701 allele and subsequently avoiding abacavir in patients with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66 of 847) to 3.4% (27 of 803) ( $p < 0.0001$ ) and the

incidence of hypersensitivity reactions confirmed by skin patch testing from 2.7% (23 of 842) to 0.0% (0 of 802) ( $p < 0.0001$ ). Based on this study, it is estimated that 48% to 61% of patients with the HLA-B\*5701 allele will develop a hypersensitivity reaction during the course of abacavir treatment compared with 0% to 4% of patients who do not have the HLA-B\*5701 allele.

Clinicians must screen for carriage of the HLA-B\*5701 allele in any HIV-infected patient prior to commencement of abacavir therapy, or prior to recommencement of abacavir therapy. Use of abacavir in patients known to carry the HLA-B\*5701 allele is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and with close medical supervision.

In any patient treated with abacavir, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision-making. Even in the absence of the HLA-B\*5701 allele, it is important to permanently discontinue abacavir and not rechallenge with abacavir if a hypersensitivity reaction cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

- **Clinical Description**

The hypersensitivity reaction is characterised by the appearance of symptoms indicating multi-organ involvement. The majority of patients have fever and/or rash as part of the syndrome.

Some of the other symptoms of hypersensitivity may include fatigue, malaise, gastrointestinal symptoms, such as nausea, vomiting, diarrhoea, or abdominal pain, and respiratory signs and symptoms such as dyspnoea, sore throat, cough and abnormal chest x-ray findings (predominantly infiltrates, which can be localised). **The symptoms of this hypersensitivity reaction can occur at any time during treatment with abacavir**, but usually occur within the first six weeks of therapy. The symptoms worsen with continued therapy and can be life threatening. These symptoms usually resolve upon discontinuation of abacavir.

- **Clinical Management**

**Patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed TRIZIVIR MUST be discontinued immediately. TRIZIVIR, or any other medicinal product containing abacavir (ZIAGEN<sup>®</sup>, KIVEXA<sup>®</sup>), MUST NEVER be restarted following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.**

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, TRIZIVIR should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). TRIZIVIR, or any other medicinal product containing abacavir (ZIAGEN<sup>®</sup>, KIVEXA<sup>®</sup>), should not be re-started even if a recurrence of

symptoms occurs following rechallenge with alternative medication(s).

An alert card with information for the patient about this hypersensitivity reaction is included in the TRIZIVIR pack.

- **Special considerations following an interruption of TRIZIVIR therapy**

If therapy with TRIZIVIR has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If hypersensitivity reaction cannot be ruled out TRIZIVIR, or any other medicinal product containing abacavir (ZIAGEN<sup>®</sup>, KIVEXA<sup>®</sup>), should not be restarted, irrespective of HLA\*B5701 carrier status.**

There have been infrequent reports of hypersensitivity reaction following reintroduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart TRIZIVIR in these patients, this should be done only under direct medical supervision.

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started abacavir therapy, and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to re-start TRIZIVIR, this must be done only if medical care can be accessed readily by the patient or others.

- **Essential patient information**

***Prescribers must ensure that patients are fully informed regarding the following information on the hypersensitivity reaction:***

- Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life threatening reaction or death.
- Patients developing signs or symptoms possibly linked with a hypersensitivity reaction **MUST CONTACT their doctor IMMEDIATELY.**
- Patients who are hypersensitive to abacavir should be reminded that they must never take TRIZIVIR or any other medicinal product containing abacavir (ZIAGEN<sup>®</sup>, KIVEXA<sup>®</sup>) again.
- In order to avoid restarting TRIZIVIR, patients who have experienced a hypersensitivity reaction should be asked to return the remaining TRIZIVIR tablets to the pharmacy.
- Patients who have stopped TRIZIVIR for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.
- Each patient should be reminded to read the Package Leaflet included

in the TRIZIVIR pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

***Lactic acidosis/severe hepatomegaly with steatosis:*** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues either alone or in combination, including abacavir, lamivudine and zidovudine. A majority of these cases have been in women. Clinical features which may be indicative of the development of lactic acidosis include generalised weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnoea and tachypnoea). Caution should be exercised when administering TRIZIVIR to any patient, and particularly to those with known risk factors for liver disease. Treatment with TRIZIVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

***Fat redistribution:*** Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, elevated serum lipid and blood glucose levels have been observed either separately or together in some patients receiving combination antiretroviral therapy (see Undesirable Effects).

Whilst all members of the PI and NRTI classes of medicinal products have been associated with one or more of these specific adverse events, linked to a general syndrome commonly referred to as lipodystrophy, data indicate that there are differences in the risk between individual members of the respective therapeutic classes.

In addition, the lipodystrophy syndrome has a multi-factorial aetiology; with for example HIV disease status, older age and duration of antiretroviral treatment all playing important, possibly synergistic roles.

The long-term consequences of these events are currently unknown.

Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

***Immune Reconstitution Syndrome:*** In HIV-infected patients with severe immune deficiency at the time of initiation of anti-retroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jirovecii*

(*P. carinii*) pneumonia. Any inflammatory symptoms must be evaluated without delay and treatment initiated when necessary.

*Patients co-infected with hepatitis C virus:* 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. Therefore, the co-administration of ribavirin and zidovudine is not advised and consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This is particularly important in patients with a known history of zidovudine induced anaemia.

***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 dosages (1200-1500mg/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 Contra-indications) in patients receiving TRIZIVIR.

These haematological effects are not usually observed before four to six weeks 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 dosage 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 <9g/dL (5.59mmol/L) or neutrophil count <1.0 x 10<sup>9</sup>/L (See Posology and Method of Administration). As dosage adjustment of TRIZIVIR is not possible separate preparations of zidovudine, abacavir and lamivudine should be used.

***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 the 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.

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

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

**Transmission of infection:** Patients should be advised that current antiretroviral therapy, including TRIZIVIR, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

**Myocardial Infarction:** In a prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous six months was correlated with an increased risk of myocardial infarction. In a pooled analysis of GSK sponsored clinical trials no excess risk of myocardial infarction was observed with abacavir use. There is no known biological mechanism to explain a potential increase. In totality the available data from observational cohorts and from controlled clinical trials are inconclusive in regard to the relationship between abacavir treatment and the risk of myocardial infarction.

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

**Concomitant medications:** Patients should be cautioned about the concomitant use of self-administered medications (see Interactions with Other Medicinal Products and Other Forms of Interaction).

**Dosage adjustment:** Separate preparations of abacavir, lamivudine and zidovudine should be administered in cases where dosage adjustment is necessary. In these cases the physician should refer to the individual prescribing information for these medicines.

### **Use During Pregnancy and Lactation**

**Pregnancy:** The safe use of TRIZIVIR in human pregnancy has not been established. Lamivudine, abacavir and zidovudine have been associated with findings in animal reproductive studies (see Pre-clinical Safety Data). Therefore administration of TRIZIVIR in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the foetus.

There have been reports of mild, transient elevations in serum lactate levels, which may be due to mitochondrial dysfunction, in neonates and infants exposed in utero or peri-partum to nucleoside reverse transcriptase inhibitors (NRTIs). The clinical relevance of transient elevations in serum lactate is unknown. There have also been very rare reports of developmental delay,

seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure in utero or peri-partum has not been established. These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

**Lactation:** Health experts recommend that where possible HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV. Both lamivudine and zidovudine are excreted in human milk at similar concentrations to those found in serum. It is expected that abacavir will also be secreted into human milk, although this has not been confirmed. It is recommended that mothers taking TRIZIVIR do not breast feed.

**Fertility:** There are no data on the affect of abacavir, lamivudine or zidovudine on human female fertility. In men zidovudine has been shown to have no effect on sperm count, morphology or motility.

### ***Effects on Ability to Drive and Use Machines***

There have been no studies to investigate the effect of TRIZIVIR, or the active components (abacavir, lamivudine and zidovudine), on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substances. 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.

### ***Interaction with Other Medicinal Products and Other Forms of Interaction***

Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine. As TRIZIVIR contains abacavir, lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur with TRIZIVIR. The interactions listed below should not be considered exhaustive but are representative of the classes of medicinal products where caution should be exercised.

### **Interactions relevant to abacavir**

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir, the potential for P<sub>450</sub> mediated interactions with other medicinal products involving abacavir is low. Abacavir shows no potential to inhibit metabolism mediated by the cytochrome P<sub>450</sub> 3A4 enzyme. Abacavir has also been shown *in vitro* not to inhibit CYP 3A4, CYP 2C9 or CYP 2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for interactions with antiretroviral protease inhibitors and other medicinal products metabolised by major P<sub>450</sub> enzymes.

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

**Methadone:** In a pharmacokinetic study, coadministration of 600mg abacavir twice daily with methadone showed a 35% reduction in abacavir  $C_{max}$  and a one hour delay in  $t_{max}$ , but AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study, abacavir increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone dose re-titration may be required.

**Retinoids:** Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interactions with abacavir are possible but have not been studied.

### **Interactions relevant to lamivudine**

The likelihood of metabolic interactions with lamivudine is low due to limited metabolism and plasma protein binding, and almost complete renal clearance. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is renal.

**Trimethoprim:** Administration of trimethoprim/sulphamethoxazole 160mg/800mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (See Posology and Method of Administration). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* (*P. carinii*) pneumonia and toxoplasmosis has not been studied.

**Zalcitabine:-** Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. TRIZIVIR is therefore not recommended to be used in combination with zalcitabine.

### **Interactions relevant to zidovudine**

Zidovudine is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. Medicinal products that are primarily eliminated by hepatic metabolism, especially via glucuronidation, may have the potential to inhibit metabolism of zidovudine.

**Lamivudine:** Co-administration of zidovudine with lamivudine results in a 13% increase in zidovudine exposure and a 28% increase in peak plasma levels. However overall exposure (AUC) is not significantly altered. This increase is not considered to be of significance to patient safety and therefore

no dosage adjustments are necessary. Zidovudine has no effect on the pharmacokinetics of lamivudine.

**Phenytoin:** Phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while in one patient a high level was noted. These observations suggest that phenytoin concentrations should be carefully monitored in patients receiving TRIZIVIR and phenytoin.

**Probenecid:** Limited data suggest that probenecid increases the mean half-life and area under the plasma concentration curve of zidovudine by decreasing glucuronidation. Renal excretion of the glucuronide (and possibly zidovudine itself) is reduced in the presence of probenecid.

**Ribavirin:** The nucleoside analogue ribavirin antagonises the *in vitro* antiviral activity of zidovudine and so concomitant use of TRIZIVIR with this medicinal product should be avoided.

**Rifampicin:** Limited data suggests that co-administration of zidovudine and rifampicin decreases the AUC of zidovudine by  $48\% \pm 34\%$ . However the clinical significance of this is unknown.

**Stavudine:** Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Stavudine is therefore not recommended for use in combination with TRIZIVIR.

Other medicinal products, including but not limited to, aspirin, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapson and isoprinosine, may alter the metabolism of zidovudine by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of interactions before using such medicinal products particularly for chronic therapy, in combination with TRIZIVIR.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (such as systemic pentamidine, dapson, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse reactions to zidovudine. 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.

Since some patients receiving TRIZIVIR may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such prophylaxis has included co-trimoxazole, aerosolised pentamidine, pyrimethamine and acyclovir. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to zidovudine with these medicinal products.

### **Undesirable Effects**

TRIZIVIR contains abacavir, lamivudine and zidovudine. The adverse events associated with these compounds listed in Table 1 below, may therefore be expected following treatment with TRIZIVIR. For many of these adverse events, it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV disease, or whether they are a result of the underlying disease process. The assessment of the safety profile of TRIZIVIR in clinical studies is not yet available.

**Hypersensitivity to abacavir** (see also Special warnings and special precautions for use):

In clinical studies, approximately 5% of subjects receiving abacavir developed a hypersensitivity reaction, which in rare cases has proved fatal. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.

Symptoms can occur at any time while being treated with abacavir, but usually appear within the first six weeks of initiation of treatment (median time to onset 11 days).

The signs and symptoms of this hypersensitivity reaction are listed below. Those reported **in at least 10% of patients** with a hypersensitivity reaction are in bold text.

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

Some patients with hypersensitivity were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity

has resulted in abacavir being continued or re-introduced, leading to a more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. If a hypersensitivity reaction can not be ruled out, TRIZIVIR, or any other medicinal product containing abacavir (ZIAGEN<sup>®</sup>, KIVEXA<sup>®</sup>) should not be restarted.

The symptoms related to this hypersensitivity reaction worsen with continued therapy, and usually resolve upon discontinuation of abacavir.

Restarting abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours. **This recurrence of the hypersensitivity reaction may be more severe than on initial presentation, and may include life-threatening hypotension and death. Patients who develop this hypersensitivity reaction must discontinue TRIZIVIR and must never be rechallenged with TRIZIVIR, or any other medicinal product containing abacavir (ZIAGEN<sup>®</sup>, KIVEXA<sup>®</sup>), irrespective of HLA\*B5701 carrier status.**

There have been infrequent reports of hypersensitivity reactions following reintroduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal or respiratory symptom).

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction.

**Table 1: Adverse events reported with the individual components of TRIZIVIR**

(Adverse events occurring in at least 5% of patients are **in bold**).

**IMPORTANT: for information on abacavir hypersensitivity, see the description above in the boxed information**

	<b>Abacavir</b>	<b>Lamivudine</b>	<b>Zidovudine</b>
<i>Cardiovascular</i>			Cardiomyopathy
<i>Gastrointestinal tract</i>	<b>Nausea, vomiting, diarrhoea.</b>	<b>Nausea, vomiting, diarrhoea, upper abdominal pain.</b>	<b>Nausea, vomiting, anorexia,</b> diarrhoea, abdominal pain, oral mucosa pigmentation, dyspepsia and flatulence.
<i>Haematological</i>		Anaemia, pure red cell aplasia, neutropenia,	Anaemia, neutropenia, leucopenia and aplastic anaemia (see below for further

<i>Liver/pancreas</i>	Pancreatitis.	thrombocytopenia.  Transient rises in liver enzymes (AST, ALT), rises in serum amylase, pancreatitis.	details), thrombocytopenia, and pancytopenia (with marrow hypoplasia) and pure red cell aplasia.  Liver disorders such as severe hepatomegaly with steatosis, rises in blood levels of liver enzymes and bilirubin, pancreatitis.
<i>Metabolic/endocrine</i>	<sup>1</sup> Lactic acidosis, hyperlactataemia  <sup>2</sup> Redistribution/accumulation of body fat	<sup>1</sup> Lactic acidosis, hyperlactataemia  <sup>2</sup> Redistribution/accumulation of body fat	<sup>1</sup> Lactic acidosis, hyperlactataemia  <sup>2</sup> Redistribution/accumulation of body fat
<i>Musculoskeletal</i>		<b>Muscle disorders</b> , rarely rhabdomyolysis arthralgia.	<b>Myalgia</b> , myopathy.
<i>Neurological/psychiatry</i>	<b>Headache.</b>	<b>Headache</b> , peripheral neuropathy, paraesthesia	<b>Headache, insomnia</b> , paraesthesia, dizziness, somnolence, loss of mental acuity, convulsions, anxiety, depression.
<i>Respiratory tract</i>			Cough, dyspnoea.
<i>Skin</i>	Rash without systemic symptoms. Very rarely erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.	<b>Rash, alopecia.</b>	Rash, nail and skin pigmentation, urticaria, pruritus, sweating.
<i>Miscellaneous</i>	<b>Fever, lethargy, fatigue, anorexia.</b>	<b>Fever, malaise, fatigue.</b>	<b>Malaise</b> , fever, urinary frequency, taste perversion, generalised pain, chills, chest pain,

			influenza-like syndrome, gynaecomastia, asthenia.
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<sup>1</sup>Lactic acidosis - see Special Warnings and Precautions for Use

<sup>2</sup>Redistribution/accumulation of body fat (see Special warnings and special precautions for use). The incidence of this event is dependent on multiple factors including the particular antiretroviral drug combination.

*Adverse events with abacavir:-*

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

*Haematological adverse events with zidovudine:-*

Anaemia (which may require transfusions), neutropenia, leucopenia and aplastic anaemia occurred more frequently at higher dosages (1200-1500mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment) and particularly in patients with CD<sub>4</sub> cell counts less than 100/mm<sup>3</sup>. Dosage reduction or cessation of therapy may become necessary (see Special warnings and precautions for use).

The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B<sub>12</sub> levels were low at the start of zidovudine therapy.

**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 undesirable effects. No fatalities occurred, and all patients recovered. Single doses up to 1200mg and daily doses up to 1800mg 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 Undesirable effects), and standard supportive treatment applied as necessary. Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdosage, 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.

For more details physicians should refer to the individual prescribing information for lamivudine, abacavir and zidovudine.

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## Pharmacological Properties

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### ***Pharmacodynamic Properties***

Pharmacotherapeutic group - nucleoside analogue.

### **Mechanism of action and resistance:-**

Lamivudine, zidovudine and abacavir are all nucleoside analogue reverse transcriptase inhibitors, 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, abacavir-TP and zidovudine-TP are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine, abacavir and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases.

Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Abacavir shows synergy *in vitro* in combination with zidovudine and has been shown to be additive in combination with lamivudine.

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo*, requiring multiple mutations to reach an eight fold increase in  $IC_{50}$  over wild-type virus, which may be a clinically relevant level. Isolates resistant to abacavir may also show reduced sensitivity to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. Treatment failure following initial combination therapy with abacavir, lamivudine and zidovudine is mainly associated with the M184V alone, thus maintaining many therapeutic options for a second line regimen.

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

Clinical experience.

In antiretroviral-naïve patients the triple combination of abacavir, lamivudine and zidovudine was superior in terms of durability of viral load response over 48 weeks to lamivudine and zidovudine. In a similar patient population durability of antiviral response over 120 weeks was demonstrated in approximately 70% of subjects.

In antiretroviral naïve patients treated with a combination of abacavir, lamivudine, zidovudine and efavirenz, 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.

In a double-blind clinical study over 48 weeks in treatment naïve adult patients, the combination of abacavir, lamivudine and zidovudine showed an equivalent antiviral effect to the combination with indinavir, lamivudine and zidovudine in the primary analysis of efficacy. In a secondary analysis of patients with baseline plasma HIV-1 RNA levels above 100,000 copies per mL, patients receiving the combination containing indinavir-had a superior response. Patients with baseline plasma HIV-1 RNA below 100,000 copies per mL had an equivalent response to both treatments.

In an ongoing clinical study over 16 weeks in treatment-naïve patients, the combination of abacavir, lamivudine and zidovudine showed a similar antiviral effect to the combination with nelfinavir, lamivudine and zidovudine.

In patients with a low baseline viral load (<5,000 copies/mL) and moderate exposure to antiretroviral therapy, addition of abacavir to previous treatment including lamivudine and zidovudine, produced a moderate impact on viral load at 48 weeks.

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 (CD<sub>4</sub> cells <50 cells/mm<sup>3</sup>).

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 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 non-nucleoside reverse transcriptase inhibitors or protease inhibitors.

### ***Pharmacokinetic Properties***

***Absorption:*** Lamivudine, abacavir and zidovudine are rapidly and well absorbed from the gastro-intestinal tract following oral administration. The absolute bioavailability of oral lamivudine, abacavir and zidovudine in adults is about 80-85%, 83% 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 COMBIVIR<sup>®</sup> and ZIAGEN<sup>®</sup> in combination were administered. The steady state parameters were also similar to the values obtained in the bioequivalence study of TRIZIVIR in healthy volunteers.

A bioequivalence study compared COMBIVIR<sup>®</sup> with lamivudine 150mg and zidovudine 300mg tablets taken together. The effect of food on the rate and extent of absorption was also studied. COMBIVIR<sup>®</sup> was shown to be bioequivalent to lamivudine 150mg and zidovudine 300mg given as separate tablets, when administered to fasting subjects.

A bioequivalence study compared TRIZIVIR with lamivudine 150mg, zidovudine 300mg and abacavir 300mg taken together. The effect of food on the rate and extent of absorption was also studied. TRIZIVIR was shown to be bioequivalent to lamivudine 150mg, zidovudine 300mg and abacavir 300mg given as separate tablets for  $AUC_{\infty}$  and  $C_{max}$ . Food decreased the rate of absorption of TRIZIVIR (slight decrease in  $C_{max}$  (mean 18 – 32%) and increased  $T_{max}$  (approximately 1 hour), but not the extent of absorption ( $AUC_{\infty}$ ). These changes are not considered clinically relevant and TRIZIVIR can be taken with or without food.

**Distribution:** Intravenous studies with lamivudine, abacavir and zidovudine showed that the mean apparent volume of distribution is 1.3, 0.8 and 1.6L/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 with medicinal products involving binding site displacement are therefore not anticipated with TRIZIVIR.

Data show that lamivudine, abacavir 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 in HIV infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%. In a Phase I pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300mg twice a day. The mean concentration of abacavir achieved in the CSF 1.5 hours post dose was 0.14mcg/mL. In a further pharmacokinetic study of 600mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0.13mcg/mL at 0.5 to 1 hour after dosing, to approximately 0.74mcg/mL after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9 fold greater than the IC50 of abacavir of 0.08mcg/mL or 0.2mM.

**Metabolism:** Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions with lamivudine is low due to the small extent of hepatic metabolism (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 less than 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the 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 0.32L/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  $\leq$  50mL/min (see Posology and method of administration).

From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6L/h/kg. Renal clearance of zidovudine is estimated to be 0.34L/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 300mg 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 populations:**

**Hepatically impaired:** 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, 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). The results showed that there was a mean increase of 1.89 fold in the abacavir AUC, and 1.58 fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates

of formation and elimination of these were decreased. Dosage reduction of abacavir is therefore required in patients with mild hepatic impairment.

The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, and is therefore contraindicated in these patient groups (see Contra-indications).

**Renally impaired:** Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction due to decreased renal clearance. Dose reduction is required for patients with creatinine clearance of <50mL/min. Zidovudine concentrations have also been shown to be increased in patients with advanced renal failure. Abacavir is primarily metabolised by the liver with less than 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.

As dosage adjustments of lamivudine and zidovudine may be necessary it is recommended that separate preparations of zidovudine, lamivudine and abacavir be administered to patients with reduced renal function (creatinine clearance <50mL/min).

**Elderly:** No pharmacokinetic data is available in patients over 65 years of age.

### **Preclinical Safety Data**

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

**Mutagenicity and carcinogenicity:** Neither lamivudine, abacavir nor zidovudine is mutagenic in bacterial tests, but like many nucleoside analogues they show activity in the *in vitro* mammalian tests such as the mouse lymphoma assay. This is consistent with the known activity of other nucleoside analogues.

Lamivudine has not shown any genotoxic activity in the *in vivo* studies. However, zidovudine and abacavir showed clastogenic effects in micronucleus tests in mice. 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. The clinical significance of these findings is unknown.

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 (420mg/kg term body weight).

In a second study, mice were administered zidovudine at doses up to 40mg/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.

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

The majority of these tumours occurred at the highest abacavir dose of 330mg/kg/day in mice and 600mg/kg/day in rats. These dose levels were equivalent to 24 to 32 times the expected systemic exposure in humans. The exception was the preputial gland tumour which occurred at a dose of 110mg/kg. This is equivalent to six times the expected human systemic exposure. There is no structural counterpart for this gland in humans. While the carcinogenic potential in humans is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.

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

*Reproductive toxicology:* In reproductive toxicity studies in animals, lamivudine, abacavir and zidovudine were all shown to cross the placenta.

Lamivudine was not teratogenic in animal studies but has shown evidence of causing an increase in early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man. The effect was not observed in the rat 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 fetuses only in rats at maternally toxic doses of 500mg/kg/day and above. This dose is equivalent to 32 to 35 times human therapeutic exposure based on AUC. The findings included foetal oedema, variations and malformations, resorptions, decreased foetal body weight and an increase in still births. The dose at which there were no effects on pre or post natal development was 160mg/kg/day. This dose is equivalent to an exposure of about 10 times that in humans. Similar findings were not observed in rabbits.

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

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## **Pharmaceutical particulars**

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### ***List of Excipients***

*Core:* microcrystalline cellulose, sodium starch glycollate, magnesium stearate.

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

### ***Incompatibilities***

Not applicable.

### ***Shelf Life***

2 years.

### ***Special Precautions for Storage***

Store below 30°C.

### ***Nature and Contents of Container***

TRIZIVIR tablets are available in HDPE bottles with child-resistant closures containing 60 tablets.

### ***Instructions for Use/Handling***

No special requirements.

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## **Medicines classification**

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Prescription Only Medicine

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## **Name and address**

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GlaxoSmithKline NZ Limited  
AMP Centre  
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## **Date of preparation**

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Issue Date: 22 January 2009

Version: 2.0

TRIZIVIR<sup>®</sup> is a registered trade mark of the GlaxoSmithKline group of companies.

## MANDATORY PACKAGING INFORMATION

### 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 ill feeling

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

#### CARTON PANEL

The following text must be included on one of the carton panels.

- **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).