CONFIDENTIAL
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PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrTRIZIVIR

abacavir (as abacavir sulfate), lamivudine and zidovudine tablets
300 mg/ 150 mg/ 300 mg

Antiretroviral Agent

ViiV Healthcare ULC
245 Boulevard Armand-Frappier
Laval, Quebec
H7V 4A7

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PrTRIZIVIR

Abacavir (as abacavir sulfate)/lamivudine/zidovudine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients[a]
Oral	Tablet/300 mg abacavir (as abacavir sulfate), 150 mg lamivudine and 300 mg zidovudine	None

a: For a complete list see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

INDICATIONS AND CLINICAL USE

TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) is indicated for the treatment of Human Immunodeficiency Virus (HIV) infection in adult patients.

Pediatrics (< 18 years of age)
The safety and effectiveness of TRIZIVIR has not been established in patients < 18 years of age.

Geriatrics (≥ 65 years of age)
Clinical studies of TRIZIVIR did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

CONTRAINDICATIONS

TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Patients who are positive for the HLA-B*5701 allele and patients with a prior history of a hypersensitivity reaction to abacavir, or products containing abacavir, regardless of HLA-B*5701 status. Fatal hypersensitivity reactions have been associated with rechallenge of abacavir (see **WARNINGS AND PRECAUTIONS**).
- Patients with hepatic impairment (due to the active ingredient abacavir).
- Patients with abnormally low neutrophil counts (< 0.75 x 10^9/L) or abnormally low hemaglobin levels (< 7.5 g/dL or 4.65 mmol/L) (due to the active ingredient zidovudine).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Fatal Hypersensitivity Reactions to Abacavir**

All patients should be screened for the HLA-B*5701 allele prior to initiating or re-initiating treatment with TRIZIVIR. Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir, a component of TRIZIVIR although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele. Serious and sometimes fatal hypersensitivity reactions have been associated with therapy with abacavir sulfate and other abacavir-containing products (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions to Abacavir).**

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including TRIZIVIR and other antiretrovirals (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).

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

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

General

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.

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.

TRIZIVIR is a fixed dose combination of three nucleoside analogues, abacavir sulfate, lamivudine and zidovudine and should not be administered concomitantly with other products containing either abacavir, lamivudine or zidovudine (ZIAGEN, 3TC, HEPTOVIR, COMBIVIR, KIVEXA, RETROVIR or TRIUMEQ) or emtricitabine containing products (ATRIPLA, EMTRIVA, TRUVADA, COMPLERA, or STRIBILD Tablets).

Hypersensitivity Reactions to Abacavir

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

Clinical Management of Abacavir HSRs

All patients should be screened for the HLA-B*5701 allele prior to initiating or re-initiating treatment with TRIZIVIR.

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

Regardless of HLA-B*5701 status, permanently discontinue TRIZIVIR if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, influenza; gastroenteritis; or reactions to other medications).

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

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

When therapy with **TRIZIVIR** has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of **TRIZIVIR** or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of **TRIZIVIR** to ensure that the patient did not have symptoms of a hypersensitivity reaction.

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

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

Clinical Description of Abacavir HSRs

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

A warning card with information for the patient about this hypersensitivity reaction is included in the TRIZIVIR outer pack label (see a copy of this card on the last page of this Product Monograph).

Carcinogenesis and Mutagenesis
Carcinogenicity studies with abacavir in mice and rats showed an increase in malignant tumours in the preputial gland of males and the clitoral gland of females of both species,

and in the liver, urinary bladder, lymph nodes and subcutis of female rats. The majority of these tumours occurred at exposures equivalent to 24 to 33 times the expected systemic exposure in humans (see **TOXICOLOGY**, **Carcinogenicity and Mutagenicity**).

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

Cardiovascular

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

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

Endocrine and Metabolism

Lipoatrophy

Treatment with zidovudine has been associated with loss of subcutaneous fat. The incidence and severity of lipoatrophy are related to cumulative exposure. This fat loss, which is most evident in the face, limbs and buttocks, may be only partially reversible and improvement may take several months when switching to a zidovudine-free regimen. Patients should be regularly assessed for signs of lipoatrophy during therapy with zidovudine and other zidovudine containing products (COMBIVIR and RETROVIR), and if feasible, therapy should be switched to an alternative regimen if there is suspicion of lipoatrophy development.

Serum lipids and blood glucose

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

Hematologic

Bone Marrow Suppression

Since TRIZIVIR contains zidovudine, TRIZIVIR should be used with extreme caution in patients who have bone marrow compromise evidenced by granulocyte count < 1,000 cells/mm^3 or hemoglobin < 9.5 g/dL. In all of the placebo-controlled studies, but most frequently in patients with advanced symptomatic disease, anemia and granulocytopenia was the most significant adverse events observed (see **ADVERSE REACTIONS**). There have been reports of pancytopenia associated with the use of zidovudine, which was reversible in most instances after discontinuation of the drug.

Very rare occurrences of pure red cell aplasia have been reported with lamivudine or zidovudine use. Discontinuation of lamivudine and/or zidovudine has resulted in normalization of hematologic parameters in patients with suspected lamivudine or zidovudine induced pure red cell aplasia.

Anemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients receiving zidovudine. These occurred more frequently at higher zidovudine dosages (1,200 to 1,500 mg/day) and in patients with poor bone marrow reserve prior to treatment, particularly with advanced HIV disease. Hematological parameters should therefore be carefully monitored in patients receiving TRIZIVIR (see **CONTRAINDICATIONS**).

These hematological 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 hematological 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 anemia or myelosuppression occurs during treatment with TRIZIVIR, or in patients with pre-existing bone marrow compromise e.g. haemoglobin less than 9 g/dl (5.59 mmol/l) or neutrophil count less than 1.0 x 10^9/l (see **DOSAGE AND ADMINISTRATION**). As dosage adjustment of TRIZIVIR is not possible separate preparations of zidovudine, abacavir and lamivudine should be used.

Hepatic/Biliary/Pancreatic

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of 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 (dyspnea and tachypnea).

Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering TRIZIVIR or other nucleoside analogues, particularly to those with known risk factors for liver disease. However, cases have also been reported in patients with no known risk factors. Treatment with TRIZIVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis with or without hepatitis, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations.

Use With Interferon and Ribavirin Based Regimens
In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine, a component of TRIZIVIR. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV/HCV co infected patients (see **DRUG INTERACTIONS**), hepatic decompensation (some fatal) has occurred in HIV/HCV co infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and TRIZIVIR should be closely monitored for treatment associated toxicities, especially hepatic decompensation. Discontinuation of TRIZIVIR should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation.

Hepatic Impariment
TRIZIVIR is contraindicated for use in hepatically impaired patients (see **CONTRAINDICATIONS**). There are no data available on the use of TRIZIVIR in hepatically impaired patients. Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because TRIZIVIR is a fixed dose combination and cannot be dose adjusted, TRIZIVIR is contraindicated for patients with hepatic impairment.

Abacavir is metabolized primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh Score A) who had confirmed cirrhosis. The results showed that there was a mean increase of 1.89 fold in the abacavir AUC, and 1.58 fold in the half life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment; therefore TRIZIVIR is contraindicated in these patient groups.

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.

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

Patients co-infected with Hepatitis C virus
Exacerbation of anemia 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 anemia.

Pancreatitis
Pancreatitis has been observed in some patients receiving nucleoside analogues, including abacavir, lamivudine and zidovudine. However it is not clear whether these cases were due to drug treatment or to the underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of TRIZIVIR until diagnosis of pancreatitis is excluded (see **ADVERSE EVENTS**, **Post-Market Adverse Drug Reactions**).

Immune

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

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

Musculoskeletal

Myopathy
Myopathy and myositis with pathological changes similar to that produced by HIV disease have been associated with prolonged use of zidovudine and therefore may occur with TRIZIVIR therapy.

Renal Impairment
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 less than 50 ml/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.

TRIZIVIR is not recommended for use in patients with a creatinine clearance < 50 mL/min as TRIZIVIR is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If patients require a dose reduction due to renal impairment, separate preparations of abacavir, lamivudine and zidovudine should be administered (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment**, and **DETAILED PHARMACOLOGY**, **Special Populations and Conditions**).

Special Populations

Pregnant Women
The safe use of TRIZIVIR in human pregnancy has not been established in adequate and well-controlled trials investigating congenital abnormalities. Therefore, TRIZIVIR should not be used in pregnant women unless the potential benefits outweigh the potential risk to the fetus.

There have been reports of developmental delay, seizures and other neurological disease. However, a causal relationship between these events and NRTI exposure *in utero* or peri-partum has not been established. Findings of developmental toxicity were also observed in animal toxicology studies (see **TOXICOLOGY**). Pregnant women considering using abacavir, lamivudine or zidovudine during pregnancy should be made aware of these findings.

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

Antiretroviral Pregnancy Registry
To monitor maternal-fetal outcomes of pregnant women exposed to ART (antiretroviral therapy), including TRIZIVIR, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients:
http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

TRIZIVIR has been evaluated in the Antiretroviral Pregnancy Registry in over 2000, 11,000, and 13,000 women respectively during pregnancy and postpartum. Available human data from the APR do not show an increased risk of major birth defects for TRIZIVIR compared to the background rate (see Clinical Studies).

The Antiretroviral Pregnancy Registry has received prospective reports of over 2,000 exposures to abacavir during pregnancy resulting in live birth. These consist of over 900 exposures during the first trimester, over 1,200 exposures during the second/third trimester and included 29 and 33 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 2.9% (2.0, 4.2%) and in the second/third trimester, 2.6% (1.8, 3.7%).

The Antiretroviral Pregnancy Registry has received reports of over 11,000 exposures to lamivudine during pregnancy resulting in live birth. These consist of over 4,500 exposures during the first trimester, over 7,200 exposures during the second/third trimester and included 143 and 207 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.1% (2.6, 3.7%) and in the second/third trimester, 2.9% (2.5, 3.3%).

The Antiretroviral Pregnancy Registry has received reports of over 13,000 exposures to zidovudine during pregnancy resulting in live birth. These consist of over 4,100 exposures during the first trimester, over 9,300 exposures during the second/third trimester and included 133 and 264 birth defects respectively. The prevalence (95% CI) of defects in the first trimester was 3.2% (2.7, 3.8%) and in the second/third trimester, 2.8% (2.5, 3.2%).

These proportions are not significantly higher than those reported in the two population based surveillance systems (2.72 per 100 live births and 4.17 per 100 live births respectively). The Antiretroviral Pregnancy Registry does not show an increased risk of major birth defects for abacavir, lamivudine or zidovudine compared to the background rates.

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

Pediatrics (< 18 years of age)
TRIZIVIR is not recommended in children. There are no data on the use of TRIZIVIR in pediatric patients (see **DETAILED PHARMACOLOGY**, **Special Populations and Conditions**, **Pediatric Patients**).

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following adverse reactions are discussed in greater detail in other sections of the labelling:

- Serious and sometimes fatal hypersensitivity reaction (see **WARNINGS AND PRECAUTIONS**, **Hypersensitivity Reactions to Abacavir**)
- Hematologic toxicity, including neutropenia and anemia (see **WARNINGS AND PRECAUTIONS, Bone Marrow Suppression**)
- Symptomatic myopathy (see **WARNINGS AND PRECAUTIONS, Myopathy**)
- Lactic acidosis and severe hepatomegaly (see **WARNINGS AND PRECAUTIONS**, **Lactic Acidosis and Severe Hepatomegaly with Steatosis**)
- Post-treatment exacerbations of hepatitis (see **WARNINGS AND PRECAUTIONS**, **Post-Treatment Exacerbations of Hepatitis B**)
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C (see **WARNINGS AND PRECAUTIONS, Use With Interferon and Ribavirin Based Regimens**)
- Exacerbation of anemia in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine (see **WARNINGS AND PRECAUTIONS, Patients co-infected with Hepatitis C virus)**

- Myocardial infarction (see **WARNINGS AND PRECAUTIONS, Cardiovascular**)
- Lipoatrophy (see **WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism**)
- Immune reconstitution inflammatory syndrome (see **WARNINGS AND PRECAUTIONS**, **Immune**)

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 Adverse events reported with the individual components of TRIZIVIR
(Adverse events occurring in at least 5% of patients are in bold)

	Abacavir	Lamivudine	Zidovudine
Cardiovascular			Cough, dyspnea
Gastrointestinal tract	**Nausea, vomiting, diarrhea**	**Nausea, vomiting, diarrhea, upper abdominal pain**	**Nausea, vomiting, anorexia**, diarrhea, abdominal pain, oral mucosa pigmentation, dyspepsia and flatulence
Hematological		Anemia, pure red cell aplasia, neutropenia, thrombocytopenia	Anemia, neutropenia, leucopenia and aplastic anemia (see text below for further details), thrombocytopenia, pancytopenia (with marrow hypoplasia) and pure red cell aplasia
Liver/pancreas	Pancreatitis	Transient rises in liver enzymes (AST, ALT), rises in serum amylase, pancreatitis	Liver disorders such as severe hepatomegaly with steatosis, rises in blood levels of liver enzymes and bilirubin, pancreatitis
Metabolic/endocrine	Lactic acidosis, hyperlactatemia	Lactic acidosis, hyperlactatemia	Lactic acidosis, hyperlactatemia Lipoatrophy
Musculoskeletal		**Muscle disorders**, rarely rhabdomyolysis arthralgia	**Myalgia,** myopathy
Neurological/psychiatry	**Headache**	**Headache**, peripheral neuropathy, paresthesia	**Headache, insomnia**, paresthesia, dizziness, somnolence, loss of mental acuity, convulsions, anxiety, depression
Respiratory tract			Cough, dyspnea
Skin	Rash without systemic symptoms. Very rarely erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis.	**Rash, alopecia**	Rash, nail and skin pigmentation, urticaria, pruritus, sweating
Miscellaneous	**Fever, lethargy, fatigue**, anorexia	**Fever, malaise, fatigue**	**Malaise,** fever, urinary frequency, taste perversion, generalized pain, chills, chest pain, influenza-like syndrome, gynecomastia, asthenia

Many of the adverse events listed above for abacavir (nausea, vomiting, diarrhea, 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.

Hematological adverse events with zidovudine
Anemia (which may require transfusions), neutropenia, leucopenia and aplastic anemia occurred more frequently at higher dosages (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 CD_4 cell counts less than $100/mm^3$. Dosage reduction or cessation of therapy may become necessary (see **WARNINGS AND PRECAUTIONS**).

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

Post-Market Adverse Drug Reactions
The following adverse reactions have been identified during use of TRIZIVIR in clinical practice. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to TRIZIVIR, or a combination of these factors.

Body as a Whole:	lipoatrophy
Cardiovascular:	cardiomyopathy
Digestive:	stomatitis
Endocrine and Metabolic:	lactic acidosis (see **WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic**, **Lactic Acidosis/Severe Hepatomegaly with Steatosis**), hyperglycemia, hyperlactemia
Gastrointestinal:	oral mucosal pigmentation
Hemic and Lymphyatic:	aplastic anemia, anemia, neutropenia, leucopenia, lymphadenopathy, pure red cell aplasia, splenomegaly
Hepatic and Pancreatic:	severe hepatomegaly with steatosis, cytolytic hepatitis, pancreatitis, posttreatment exacerbation of hepatitis B
Hypersensitivity:	sensitization reactions (including anaphylaxis), urticaria
Immune System:	Immune Reconstitution Inflammatory Syndrome (see **WARNINGS AND PRECAUTIONS**, **Immune**)
Musculoskeletal:	myalgia, arthralgia, CPK elevation, rhabdomylosis
Miscellaneous:	gynecomastia, asthenia
Nervous:	paresthesia, peripheral neuropathy, seizures
Respiratory:	abnormal breath sounds/wheezing, respiratory failure
Skin:	alopecia, **erythema multiforme**, **Stevens-Johnson Syndrome**, **toxic epidermal necrolysis**

Description of Abacavir Hypersensitivity Adverse Reactions

Hypersensitivity

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

As described in Warnings and Precautions, almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however, reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

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

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

DRUG INTERACTIONS

Overview
As TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) contains abacavir, lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur with TRIZIVIR. Clinical studies have shown that there are no clinically significant interactions between abacavir sulfate, zidovudine and lamivudine.

Effect of Abacavir on the Pharmacokinetics of Other Agents

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

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

Effect of Other Agents on the Pharmacokinetics of Abacavir

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

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

Interactions Relevant to Abacavir

Abacavir and lamivudine are not significantly metabolized 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 metabolized by major P_{450} enzymes.

Effect of Lamivudine on the Pharmacokinetics of Other Agents

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

Lamivudine is an inhibitor of OCT1 and OCT2 *in vitro* with IC50 values of 17 and 33 μM, respectively, however lamivudine has low potential to affect the plasma

concentrations of OCT1 and OCT2 substrates at therapeutic drug exposures (up to 300 mg).

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

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

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

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. Lamivudine is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is renal.

Interactions Relevant to Zidovudine
Medicinal products, including but not limited to, acetylsalicylic acid, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate 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, pyrimethamine, co-trimoxazole, amphotericin, ganciclovir and interferon) 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 hematological parameters and, if required, the dosage of one or more agents should be reduced.

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, aerosolized 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.

Drug-Drug Interactions

No drug interaction studies have been conducted with TRIZIVIR. The drugs listed in the following table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 2 Established or Potential Drug-Drug Interactions

Abacavir Drug Interactions		
Proper name	**Effect**	**Clinical comment**
Ethanol	In men, the metabolism of abacavir sulfate is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%.	The clinical significance of this is unknown. In men, abacavir sulfate has no effect on the metabolism of ethanol. This interaction has not been studied in women.
Methadone	In a pharmacokinetic study, coadministration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir C_{max} and a one hour delay in t_{max}, but AUC was unchanged.	The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study, abacavir increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone re-titration may be required.
Retinoids		Retinoid compounds, such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.
Lamivudine Drug Interactions		
Proper name	**Effect**	**Clinical comment**
Emtricitabine	Lamivudine may inhibit the intracellular phosphorylation of emtricitabine when the two medicinal products are used concurrently. Additionally, the mechanism of viral resistance for both lamivudine and emtricitabine is mediated via mutation of the same viral reverse transcriptase gene (M184V) and therefore the therapeutic efficacy of these drugs in combination therapy may be limited.	TRIZIVIR is not recommended for use in combination with emtricitabine or emtricitabine-containing fixed-dose combinations.

Ribavirin	*In vitro* data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine.	No pharmacokinetic (e.g. plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g. loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi drug regimen to HIV/HCV coinfected patients (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).
Sorbitol	Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC_{∞}) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults.	When possible, avoid chronic coadministration of sorbitol-containing medicines with lamivudine. Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided.
Trimethoprim	Administration of trimethoprim/ sulphamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component.	Unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary (see **DOSAGE AND ADMINISTRATION**). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. The effect of co-administration of lamivudine with higher doses of co-trimoxazole used for the treatment of *Pneumocystis jiroveci* pneumonia (often referred to as PCP) and toxoplasmosis has not been studied.

Zidovudine Drug Interactions

Proper name	**Effect**	**Clinical comment**
Atovaquone	Zidovudine does not appear to affect the pharmacokinetics of atovaquone.	Pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a three week, concomitant course of atovaquone for the treatment of acute PCP would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine. Extra care should be taken in monitoring patients receiving prolonged atovaquone therapy.
Bone marrow suppressive agents/cytotoxic agents	Coadministration may increase risk of hematologic toxicity.	Coadministration of zidovudine with drugs that are cytotoxic or which interfere with RBC/WBC number or function (e.g. dapsone, flucytosine, vincristine, or adriamycin) may increase the risk of hematologic toxicity.

Clarithromycin	Clarithromycin tablets reduce the absorption of zidovudine.	This can be avoided by separating the administration of zidovudine and clarithromycin by at least two hours.
Fluconazole	Fluconazole interferes with the oral clearance and metabolism of zidovudine.	Preliminary data suggests that fluconazole interferes with the oral clearance and metabolism of zidovudine. In a pharmacokinetic interaction study in which 12 HIV-positive men received zidovudine alone and in combination with fluconazole, increases in the mean peak serum concentration (79%), AUC (70%) and half-life (38%) were observed at steady state. The clinical significance of this interaction is unknown.
Interferon-alpha	Hematologic toxicities have been seen when RETROVIR (AZT) is used concomitantly with interferon-alpha.	As with the concomitant use of RETROVIR (AZT) and ganciclovir, dose reduction or interruption of one or both agents may be necessary, and hematologic parameters should be monitored frequently.
Lamivudine	Coadministration resulted in a 13% increase in C_{max} of zidovudine and a 28% increase in peak plasma levels.	Zidovudine and lamivudine were coadministered to 12 asymptomatic HIV-positive patients in a single-center, open-label, randomized, crossover study. No significant differences were observed in AUC_{∞} or total clearance for lamivudine or zidovudine when the two drugs were administered together. Coadministration of zidovudine with lamivudine resulted in an increase of 39% ± 62% (mean ± SD) in C_{max} of zidovudine. This increase is not considered significant to patient safety and therefore no dosage adjustments are necessary.
Methadone	Plasma levels of zidovudine can be elevated in some patients while remaining unchanged in others.	In a pharmacokinetic study of 9 HIV-positive patients receiving methadone-maintenance (30 to 90 mg daily) concurrent with 200 mg of zidovudine every 4 hours, no changes were observed in the pharmacokinetics of methadone upon initiation of therapy with zidovudine and after 14 days of treatment with zidovudine. No adjustments in methadone-maintenance requirements were reported. However, plasma levels of zidovudine were elevated in some patients while remaining unchanged in others. The exact mechanism and clinical significance of these data are unknown.

Phenytoin	A decrease in oral zidovudine clearance.	Phenytoin plasma levels have been reported to be low in some patients receiving zidovudine, while in one case a high level was documented. However, in a pharmacokinetic interaction study in which 12 HIV-positive volunteers received a single 300 mg phenytoin dose alone and during steady-state zidovudine conditions (200 mg every 4 hours), no change in phenytoin kinetics was observed. Although not designed to optimally assess the effect of phenytoin on zidovudine kinetics, a 30% decrease in oral zidovudine clearance was observed with phenytoin.
Probenecid	May increase zidovudine levels.	Limited data suggest that probenecid may increase zidovudine levels by inhibiting glucuronidation and/or reducing renal excretion of zidovudine. Some patients who have used zidovudine concomitantly with probenecid have developed flu-like symptoms consisting of myalgia, malaise, and/or fever and maculopapular rash.
Ribavarin	Coadministration of ribavirin and zidovudine may lead to increased ribavirin levels and increased risk of anemia.	Preliminary data suggest that the use of ribavirin and zidovudine lead to increased ribavirin levels and increased risk of anemia. The use of ribavirin concomitantly with zidovudine in the treatment of HIV / Hep C co-infected patients is not advised. Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established.
Stavudine	Zidovudine may inhibit intracellular phosphorylation of stavudine	Zidovudine may inhibit the intracellular phosphorylation of stavudine when the two medicinal products are used concurrently. Stavudine is therefore not recommended to be used in combination with zidovudine.
Valproic acid	Increase in zidovudine AUC and a decrease in the plasma GZDV AUC.	The concomitant administration of valproic acid 250 mg (n=5) or 500 mg (n=1) every 8 hours and zidovudine 100 mg orally every 8 hours for 4 days to 6 HIV-infected, asymptomatic male volunteers resulted in a 79% ± 61% (mean ± SD) increase in the plasma zidovudine AUC and a 22% ± 10% decrease in the plasma GZDV AUC as compared to the administration of zidovudine in the absence of valproic acid. The GZDV/zidovudine urinary excretion ratio decreased 58% ± 12%. Because no change in the zidovudine plasma half-life occurred, these results suggest that valproic acid may increase the oral bioavailability of zidovudine through inhibition of first-pass metabolism. Although the clinical signification of this interaction is unknown, patients should be monitored more closely for a possible increase in zidovudine-related adverse effects. The effect of zidovudine on the pharmacokinetics of valproic acid was not evaluated.

Other agents		Some drugs such as trimethoprim-sulfamethoxazole, pyrimethamine, and acyclovir may be necessary for the management or prevention of opportunistic infections. In the placebo-controlled trial in patients with advanced HIV disease, increased toxicity was not detected with limited exposure to these drugs. However, there is one published report of neurotoxicity (profound lethargy) associated with concomitant use of zidovudine and acyclovir. Preliminary data from a drug interaction study (n=10) suggest that coadministration of 200 mg zidovudine and 600 mg rifampin decreases the area under the zidovudine plasma concentration curve by an average of 48% ± 34%. However, the effect of once daily dosing of rifampin on multiple daily doses of zidovudine is unknown.
Miscellaneous		Other medicinal products, including but not limited to, acetylsalicyclic acid, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone 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, dapsone, 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 hematological parameters and, if required, the dosage of one or more agents should be reduced.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) can be taken with or without food.

Recommended Dose and Dosage Adjustment

Because TRIZIVIR is a fixed dose tablet it should not be prescribed for patients requiring dosage adjustments, such as:

- patients with renal impairment (creatinine clearance < 50 mL/min)
- patients who weigh less than 40 kg
- patients experiencing dose-limiting adverse events

Separate preparations of abacavir (ZIAGEN), lamivudine (3TC) or zidovudine (RETROVIR) should be administered in cases where discontinuation or dose adjustment is indicated.

Adults (≥ 18 years)

The recommended dose of TRIZIVIR is one tablet twice daily. One tablet contains 300mg of abacavir (as abacavir sulfate), 150 mg of lamivudine, and 300 mg of zidovudine.

Special Populations

Pediatrics (< 18 years)

The safety and effectiveness of TRIZIVIR have not been established in patients less than 18 years of age.

Geriatrics (≥ 65 years of age)

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

Hepatic Impairment

Dosage adjustments for both abacavir and zidovudine may be required in patients with mild hepatic impairment (Child-Pugh Score A). As dose reduction is not possible with TRIZIVIR, the separate preparations of abacavir (ZIAGEN), lamivudine (3TC) and zidovudine (RETROVIR) should be used when this is judged necessary. TRIZIVIR is contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh Score B or C) (see **WARNINGS AND PRECAUTIONS**, **Hepatic Impairment**).

Missed Dose

It is important to take TRIZIVIR as prescribed to ensure the patient gets maximum benefit. If the patient forgets to take a dose, they should take it as soon as they remember, and then continue as before. Patients must not take more than one tablet to make up for forgotten individual doses.

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

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

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

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

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

Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, while elimination of its primary metabolite, GZDV is enhanced.

Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered.

Single doses up to 1,200 mg and daily doses up to 1,800 mg of abacavir sulfate have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. No specific signs or symptoms have been identified following such overdose.

Cases of acute overdose of zidovudine in both children and adults have been reported with doses up to 50 grams. The only consistent finding in these cases of overdosage was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not severe. Some patients experienced non specific CNS symptoms such as headache, dizziness, drowsiness, lethargy, and confusion. One report of a grand mal seizure possible attributable to zidovudine occurred in a 35-year old male, 3 hours after ingesting 36 grams of zidovudine. No other causes could be identified. All patients recovered without permanent sequelae.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) is a fixed dose combination of three nucleoside analogues (abacavir, lamivudine and zidovudine). Abacavir is a carbocyclic synthetic nucleoside analogue of deoxyguanosine-5'-triphosphate. Lamivudine is also a synthetic nucleoside analogue, an (-) enantiomer of a dideoxy analogue of cytidine. Zidovudine is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Abacavir, lamivudine and zidovudine are metabolized sequentially by intracellular kinases to their respective triphosphate (TP), which are the active moieties (carbovir-triphosphate (CBV-TP) for abcavir, lamivudine triphosphate (L-TP) for lamivudine and zidovudine triphosphate (ZDV-TP) for zidovudine). Abacavir sulfate, lamivudine and zidovudine are nucleoside reverse transcriptase inhibitors (NRTIs), and are potent, selective inhibitors of HIV-1 and HIV-2 replication *in vitro*. *In vitro* L-TP and ZDV-TP have an intracellular half-life of approximately 10.5 to 15.5 hours and 3 hours respectively. CBV-TP, L-TP and ZDV-TP are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). Inhibition of RT is via viral DNA chain termination after nucleoside analogue incorporation. CBV-TP, L-TP and ZDV-TP show significantly less affinity for host cell DNA polymerases and are weak inhibitors of mammalian α, β and γ-DNA polymerases.

Pharmacokinetics (individual components)

Abacavir

Abacavir sulfate is rapidly and well absorbed following oral administration. The absolute bioavailability of oral abacavir sulfate in adults is about 83%. Following oral administration, the mean time (t_{max}) to maximal serum concentrations of abacavir is about 1.5 hours for the tablet formulation and about 1.0 hour for the solution formulation. There are no differences observed between the AUC for the tablet or solution. At therapeutic dosages (300 mg twice daily), the steady state C_{max} of abacavir sulfate tablets is approximately 3 μg/mL, and the AUC over a dosing interval of 12 hours is approximately 6 μg.h/mL. The C_{max} value for the oral solution is slightly higher than the tablet. Food delayed absorption and decreased C_{max} but did not affect overall plasma concentrations (AUC). Therefore abacavir can be taken with or without food.

Lamivudine

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected adult patients after administration of single oral, multiple oral and intravenous (IV) doses ranging from 0.25 to 10 mg/kg. After oral administration lamivudine is well absorbed from the gut. The bioavailability of lamivudine in adults is normally between 80 and 85% and the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. After oral administration of 2 mg/kg, the peak plasma lamivudine concentration (C_{max}) was 1.5 ± 0.5 μg/mL (mean ± S.D.) and half-life was 2.6 ± 0.5 hours. There were no significant differences in half-life across the range of single doses (0.25 to 8 mg/kg). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to dose over the range from 0.25 to 10 mg/kg.

Zidovudine
Pharmacokinetic studies of zidovudine following intravenous dosing in adults indicate dose-independent kinetics over the range of 1 to 5 mg/kg with a mean zidovudine half-life of 1.1 hours. Zidovudine is rapidly metabolized in the liver to 3'-azido-3'-deoxy-5'-O-β-D- glucopyranuronosylthymidine (GZDV, formerly called GAZT), and both are rapidly eliminated by the kidney. A second metabolite, 3'-amino-3'-deoxythymidine (AMT) has been identified in the plasma following single dose intravenous administration of zidovudine. After oral dosing in adults, zidovudine is rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours, with an average oral bioavailability of 65%.

STORAGE AND STABILITY

Store TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) tablets between 15° and 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) tablets are blue/green, capsule-shaped, film-coated tablets imprinted with GX LL1 on one face containing 300 mg abacavir as abacavir sulfate, 150 mg lamivudine and 300 mg zidovudine. Available in HDPE bottles of 60.

Composition
Each TRIZIVIR tablet contains 300 mg of abacavir (as 351 mg abacavir sulfate), 150 mg of lamivudine and 300 mg of zidovudine. In addition, each tablet contains the following non-medicinal ingredients; hydroxypropyl methyl cellulose, indigotine aluminium lake, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

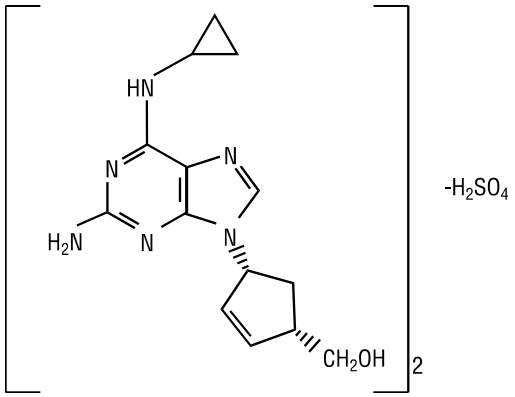
Drug Substance

Proper name: abacavir sulfate

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

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

Structural formula:



Physicochemical properties:

Physical Form: Abacavir sulfate is a white to off-white powder.

Solubility: The aqueous solubility and pH of abacavir sulfate was determined at 25°C as follows:

Solvent	Solubility (mg/mL)	pH
Distilled water	77	3.1
0.1 M HCl	110	1.6
0.1 M NaOH	22	12.2

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

Melting point: 219°C followed by decomposition.

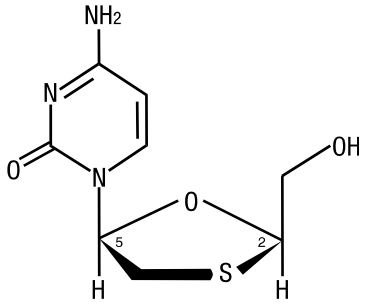
Drug Substance

Proper name: lamivudine

Chemical name: 2(1H)-Pyrimidinone,4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-,(2R-cis)-

Molecular formula and molecular mass: $C_8H_{11}N_3O_3S$ 229.3

Structural formula:



Physicochemical properties:

Physical Form: Lamivudine is a white to off-white crystalline solid.

Solubility: ~70 mg/mL in water at 20°C.

pKa and pH: The pK_a determined by UV is 4.30. The pH value of a 1% w/v solution of lamivudine in water is approximately 6.9.

Partition coefficient: The distribution coefficient of lamivudine between n-octanol and water at pH 7.4 was -0.7± 0.2 when measured by HPLC.

Melting point: 176°C.

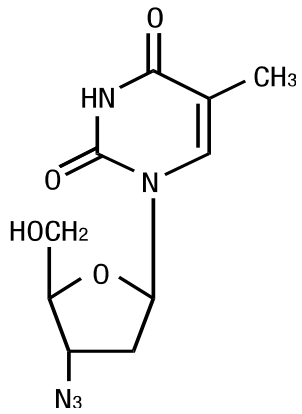
Drug Substance

Proper name: zidovudine

Chemical name: 3'-azido-3'-deoxythymidine

Molecular formula and molecular mass: $C_{10}H_{13}N_5O_4$ 267.24

Structural formula:



Physicochemical properties:

Physical Form: Zidovudine is a white to beige, odourless, crystalline solid.

Solubility: 20.1 mg/mL at 25°C in water.

pKa and pH: The pKa is 9.68. The pH value of a 10 mg/L solution of zidovudine in water is approximately 6.2.

Partition coefficient: The distribution coefficient of zidovudine between 1-octanol and distilled water at 25°C is 1.15.

Melting point: 122-124°C.

CLINICAL TRIALS

CNA3005

CNA3005 was a multicentre, double-blind study in which 562 HIV-1 infected, therapy-naïve adults were randomized to receive either ZIAGEN (300 mg twice daily) and COMBIVIR (lamivudine, 150 mg and zidovudine, 300 mg twice daily) or indinavir (800 mg three times daily) and COMBIVIR (twice daily) for 48 weeks. All subjects were required to adhere to the TID regimen and food/water restrictions. Study participants were predominantly male (87%) and Caucasian (73%).

The median age was 35.7 years, the median pretreatment CD_4 cell count was 360 cells/mm^3, and median plasma HIV-1 RNA was 4.83 log_{10} copies/mL.

Over 48 weeks, treatment of naïve adult patients, with the combination of abacavir, lamivudine and zidovudine showed a similar antiviral effect to the combination with indinavir, lamivudine and zidovudine when 400 copies/mL was the threshold used. In a secondary analysis of patients with baseline plasma HIV-1-RNA levels above 100,000 copies/mL and when the ultrasensitive assay was used to determine the proportion of patients with less than 50 copies/mL, patients receiving the combination containing indinavir had a superior response.

Comparative Bioavailability Studies

The single-dose pharmacokinetic properties of TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) have been studied in 24 healthy adult subjects in a single-centre, open-label, randomized, three-way crossover study to evaluate the bioequivalence between TRIZIVIR and the 300 mg abacavir tablet, 150 mg lamivudine tablet and the 300 mg zidovudine tablet given simultaneously. TRIZIVIR was bioequivalent to one abacavir tablet (300 mg) plus one lamivudine tablet (150 mg) plus one zidovudine tablet (300 mg) when administered to fasting subjects. A summary of the results is provided in Table 3.

Table 3 Summary Table of the Comparative Bioavailability Data for Single Dose Studies for TRIZIVIR (abacavir, lamivudine and zidovudine) tablets

	Geometric Mean and Arithmetic Mean (CV)									Ratio of Geometric Means A:B (90% CI)			Ratio of Geometric Means C:A (90% CI)		
	Treatment A Combined Abacavir 300 mg, Lamivudine 150 mg and Zidovudine 300 mg Tablet Fasted			Treatment B Abacavir 300 mg Tablet + Lamivudine 150 mg Tablet + Zidovudine 300 mg Tablet Fasted			Treatment C Combined Abacavir 300 mg, Lamivudine 150 mg and Zidovudine 300 mg Tablet Fed								
	ABC	LAM	ZDV	ABC	LAM	ZDV	ABC	LAM	ZDV	ABC	LAM	ZDV	ABC	LAM	ZDV
AUC_∞ (µg.h/mL)	6.87 7.31 (37)	5.92 6.06 (23)	1.97 2.07 (35)	6.92 7.39 (38)	6.23 6.45 (27)	2.08 2.17 (33)	6.27 6.57 (32)	5.47 5.61 (24)	1.99 2.05 (26)	0.99 (0.96, 1.03)	0.95 (0.91, 0.99)	0.95 (0.89, 1.02)	0.91 (0.88, 0.95)	0.92 (0.88, 0.97)	1.01 (0.94, 1.08)
AUC_{last} (µg.h/mL)	6.77 7.22 (37)	5.76 5.91 (23)	1.96 2.06 (35)	6.83 7.30 (38)	6.09 6.31 (28)	2.06 2.16 (34)	6.17 6.47 (32)	5.33 5.48 (25)	1.98 2.04 (26)	0.99 (0.95, 1.03)	0.95 (0.90, 0.99)	0.95 (0.89, 1.02)	0.91 (0.88, 0.95)	0.93 (0.88, 0.97)	1.01 (0.94, 1.08)
C_{max} (µg/mL)	3.10 3.29 (38)	1.49 1.57 (31)	1.24 1.36 (54)	3.10 3.23 (30)	1.66 1.78 (41)	1.29 1.43 (48)	2.12 2.28 (37)	1.22 1.27 (29)	0.89 0.99 (51)	1.00 (0.90, 1.11)	0.90 (0.82, 0.99)	0.96 (0.80, 1.15)	0.68 (0.62, 0.76)	0.82 (0.75, 0.90)	0.72 (0.60, 0.87)
T_{max}* (h)	0.75 0.96 (59)	1.25 1.35 (41)	0.75 0.84 (62)	0.75 0.74 (51)	1.00 1.34 (59)	0.75 0.84 (52)	2.00 1.93 (44)	2.50 2.40 (32)	1.50 1.70 (51)	0.13 (0.00, 0.38)	0.13 (-0.13, 0.25)	0.00 (-0.23, 0.13)	0.98 (0.63, 1.25)	1.00 (0.75, 1.38)	0.86 (0.61, -.13)
T ½ (h)	1.58 1.69 (42)	6.16 6.47 (36)	2.40 2.50 (32)	1.57 1.68 (43)	6.05 6.21 (25)	2.21 2.29 (28)	1.86 1.96 (35)	5.57 5.69 (22)	2.48 2.63 (41)	1.01 (0.90, 1.13)	1.02 (0.92, 1.12)	1.09 (0.94, 1.25)	1.17 (1.04, 1.32)	0.90 (0.82, 1.00)	1.03 (0.90, 1.19)

* Median on T_{max}. T_{max} was analyzed using Wilcoxon Signed Rank. Ratio and Confidence Intervals are to median difference.

DETAILED PHARMACOLOGY

Pharmacokinetics in Adults

The single-dose pharmacokinetic properties of TRIZIVIR (abacavir/lamivudine/zidovudine) have been studied in 24 healthy adult subjects in a single-center, open-label, randomized, three-way crossover study to evaluate the bioequivalence between TRIZIVIR and the 300 mg abacavir tablet, 150 mg lamivudine tablet and the 300 mg zidovudine tablet given simultaneously. The effect of food (67 g fat, 33 g protein and 58 g carbohydrate) on the rate and extent of absorption of TRIZIVIR was also evaluated (see **Effect of Food on Absorption**). TRIZIVIR was bioequivalent to

one abacavir tablet (300 mg) plus one lamivudine tablet (150 mg) plus one zidovudine tablet (300 mg) when administered to fasting subjects.

Absorption and Bioavailability

Abacavir sulfate was rapidly and extensively absorbed after oral administration. Absolute bioavailability of the tablet was 86% ± 25% (mean ± SD). After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{max}) was 3.0 ± 0.89 μg/mL (mean ± SD) and AUC $_{(0\text{-}12\ hours)}$ was 6.02 ± 1.73 μg•h/mL.

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the tablet and 87% ± 13% for the oral solution.

After oral dosing (capsules) zidovudine was rapidly absorbed from the gastrointestinal tract. As a result of first-pass metabolism, the average oral capsule bioavailability of zidovudine is 64% ± 10% (mean ± SD).

Distribution

Following intravenous administration, the apparent volume of distribution of abacavir was about 0.8 L/kg, indicating that abacavir penetrates freely into body tissues. Lamivudine apparent volume of distribution after intravenous (IV) administration to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight. 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 drug interactions through plasma protein binding displacement. Binding of lamivudine to human plasma proteins is low (< 36%). *In vitro* studies showed that, over the concentration range of 0.1 to 100 μg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration. Similar to lamivudine, zidovudine apparent volume of distribution after IV administration was 1.6 L/kg and plasma protein binding is 34% to 38%.

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 300 mg twice a day. The mean concentration of abacavir achieved in the CSF 1.5 hours post dose was 0.14 μg/mL. In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0.13 μg/mL at 0.5 to 1 hour after dosing, to approximately 0.74 μg/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 IC_{50} of abacavir of 0.08 μg/mL or 0.26 μM. However, no effect on neuropsychological performance was seen when administered to patients with AIDS Dementia Complex.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF lamivudine concentrations in eight patients ranged from 5.6% to 30.9% (mean ± SD of 14.2% ± 7.9%) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.30 μg/mL. The zidovudine CSF/plasma concentration ratio was determined in 39 adult patients receiving chronic therapy with zidovudine. The median ratio measured in 50 paired samples drawn 1 to 8 hours after the last dose of zidovudine was 0.6 (range 0.04 to 2.62).

Metabolism

The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the 5'-glucuronide). The metabolites do not have antiviral activity. *In vitro* experiments reveal that abacavir had weak inhibition of human CYP3A4, CYP2D6 or CYP2C9 activity at clinically relevant concentrations. In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes.

Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral lamivudine dose in six HIV-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Zidovudine is rapidly metabolized to 3'-azido-3'-deoxy-5'-O-β-D-glucopyranuronosylthymidine (GZDV) which has an apparent elimination half life of 1 hour (range 0.61 to 1.73 hours). Following oral administration, urinary recovery of zidovudine and GZDV accounted for 14% and 74% of the dose, respectively, and the total urinary recovery averaged 90% (range 63% to 95%), indicating a high degree of absorption. A second metabolite, 3'-amino-3'-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous administration of zidovudine.

AMT area-under-the-curve (AUC) was one-fifth of the AUC of zidovudine and had a half life of 2.7 ± 0.7 hours. In comparison, GZDV AUC was about three fold greater than the AUC of zidovudine.

Elimination

Elimination of abacavir was quantified in a mass balance study following administration of a 600mg dose of ^{14}C-abacavir, 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5'-carboxylic acid metabolite, 36% as the 5'-glucuronide metabolite and 15% as the unidentified minor metabolite in the urine. Fecal elimination accounted for 16% of the dose. In single-dose studies, the observed elimination half-life $t_{1/2}$ was 1.54 ± 0.63 hours. Total clearance was 0.84 ± 0.24 L/hr/kg (mean ± SD).

The majority of lamivudine is eliminated unchanged in urine. In 20 patients given a single IV dose, renal clearance was 0.22 ± 0.06 L/hr/kg (mean ± SD), representing 71% ± 16% (mean ± SD) of total lamivudine clearance. In most single-dose studies in HIV-infected patients with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. Oral clearance was 0.37 ± 0.05 L/hr/kg (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg. Renal clearance is estimated to be 314 mL/min, indicating glomerular filtration and active tubular secretion by the kidneys.

Zidovudine pharmacokinetic data following intravenous dosing indicated dose independent kinetics over the range of 1 to 5 mg/kg with a mean zidovudine half life of 1.1 hours (range 0.48 to 2.86 hours). Total body clearance averaged 1.6 L/hr/kg. Renal clearance is estimated to be 0.34 L/hr/kg, indicating glomerular filtration and active tubular secretion by the kidneys.

Special Populations and Conditions

Impaired Renal Function

The elimination of lamivudine and zidovudine in patients with impaired renal function is diminished. Reduction of the dosages of lamivudine and zidovudine are recommended for patients with impaired renal function (see **WARNINGS AND PRECAUTIONS**).

The pharmacokinetic properties of abacavir have been studied in 6 end stage renal disease patients. Abacavir concentration were similar to those with normal renal function. The two major metabolites (5'-glucuronide and 5'-carboxylate metabolites) are likely to accumulate but are considered inactive.

The pharmacokinetic properties of lamivudine were determined in a small group of HIV-infected adults with impaired renal function, and are summarized in Table 4.

Table 4 Pharmacokinetic Parameters (Mean ± S.D.) After a Single 300 mg Oral Dose of Lamivudine in Three Groups of Adults With Varying Degrees of Renal Function (CrCl > 60 mL/min, CrCl = 10-30 mL/min, and CrCl < 10mL/min)

Number of subjects	6	4	6
Creatinine clearance criterion	> 60 mL/min	10-30 mL/min	< 10 mL/min
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (µg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC_{∞} (µg·h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

These results show increases in C_{max} and half life with diminishing creatinine clearance. Apparent total clearance (Cl/F) of lamivudine decreased as creatinine clearance

decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with reduced creatinine clearance (see **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of zidovudine have been evaluated in patients with impaired renal function following a single 200 mg oral dose. In 14 patients (mean creatinine clearance 18 ± 2 mL/min), the half-life of zidovudine was 1.4 hours compared to 1.0 hour for control subjects with normal renal function; AUC values were approximately twice those of controls. Additionally, GZDV half life in these patients was 8.0 hours (vs 0.9 hours for control) and AUC was 17 times higher than for control subjects. The pharmacokinetics and tolerance were evaluated in a multiple dose study in patients undergoing hemodialysis (n=5) or peritoneal dialysis (n=6). Patients received escalating doses of zidovudine up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated plasma levels of GZDV. Total body clearance after oral administration of zidovudine was approximately 50% of that reported in patients with normal renal function. The plasma concentrations of AMT are not known in patients with renal insufficiency. Daily doses of 300 to 400 mg should be appropriate in HIV infected patients with severe renal dysfunction. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of zidovudine, whereas GZDV elimination is enhanced.

Pregnancy
The pharmacokinetics of zidovudine have been studied in a Phase 1 study of eight women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. The pharmacokinetics of zidovudine were similar to those in nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in infant plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in five pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see **DRUG INTERACTIONS**).

Following oral administration, lamivudine pharmacokinetics in late-pregnancy were similar to non-pregnant adults.

Pediatric Patients
TRIZIVIR has not been studied in pediatric patients.

Geriatric Patients
Abacavir, lamivudine and zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Gender
The pharmacokinetics of abacavir with respect to gender have not been determined. There are no significant differences in pharmacokinetic properties of lamivudine or zidovudine by gender.

Race
The pharmacokinetics of abacavir and zidovudine with respect to race have not been determined. There are no significant differences in pharmacokinetic properties of lamivudine among races.

Effect of Food on Absorption
TRIZIVIR may be administered with or without food. Administration of food in the single-dose, bioavailability study resulted in a slightly lower C_{max} and an increase in T_{max}, similar to results observed for the reference formulations. The extent of abacavir, lamivudine and zidovudine AUC following administration of TRIZIVIR with food was similar when compared to fasting healthy subjects (n = 24).

MICROBIOLOGY

In Vitro Activity

Abacavir
The *in vitro* anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1 IIIB in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1 BaL in primary monocytes/macrophages and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μM against HIV-1 IIIB, and was 0.26 ± 0.18 μM (1 μM = 0.28 μg/mL) against eight clinical isolates. The IC_{50} of abacavir against HIV-1 BaL varied from 0.07 to 1.0 μM. The antiviral activity of abacavir in cell culture was not antagonized when combined with the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine or zidovudine, the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, or the protease inhibitor (PI) amprenavir.

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

Zidovudine
Zidovudine blocked 90% of detectable HIV replication *in vitro* at concentrations of ≤ 0.13 μg/mL (ID_{90}) when added shortly after laboratory infection of susceptible cells. This level of antiviral effect was observed in experiments measuring reverse transcriptase

activity in HIV-infected H9 cells, PHA stimulated peripheral blood lymphocytes, and unstimulated peripheral blood lymphocytes. The concentration of drug required to produce a 50% decrease in supernatant reverse transcriptase was 0.013 μg/mL (ID_{50}) in both HIV-infected H9 cells and peripheral blood lymphocytes. Zidovudine at concentrations of 0.13 μg/mL also provided > 90% protection from a strain of HIV (HTLV IIIB) induced cytopathic effects in two tetanus-specific T_4 cell lines. HIV-p24 antigen expression was also undetectable at the same concentration in these cells. Partial inhibition of viral activity in cells with chronic HIV infection (presumed to carry integrated HIV DNA) required concentrations of zidovudine (8.8 μg/mL in one laboratory to 13.3 μg/mL in another) which are approximately 100 times as high as those necessary to block HIV replication in acutely infected cells. HIV isolates from 18 untreated individuals with AIDS or ARC had ID_{50} sensitivity values between 0.003 to 0.013 μg/mL and ID_{95} sensitivity values between 0.03 to 0.3 μg/mL. No antagonistic effects *in vitro* were seen with zidovudine and other antiretrovirals (tested agents: abacavir, didanosine, lamivudine and interferon-alpha).

Drug Resistance

Abacavir
Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the RT codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly *in vitro* and *in vivo*, requiring multiple mutations to reach an eight fold increase in IC_{50} over wild type virus, which may be a clinically relevant level. The mutations selected by *in vitro* passage have also been observed among isolates obtained from patients participating in clinical trials, with L74V and M184V being the most common. Combination therapy with ZIAGEN (abacavir sulfate) and zidovudine delays the emergence of mutations associated with resistance to ZIAGEN compared with monotherapy with ZIAGEN.

Lamivudine
In nonclinical studies, lamivudine-resistant isolates of HIV have been selected *in vitro*. A known mechanism of lamivudine resistance is the change in the 184 amino acid of RT from methionine to either isoleucine or valine. *In vitro* studies indicate that zidovudine-resistant viral isolates can become sensitive to zidovudine when they acquire the 184 mutation. The clinical relevance of such findings remains, however, not well defined.

For isolates collected in clinical studies, phenotypic resistance data showed that resistance to lamivudine monotherapy developed within 12 weeks. Evidence in isolates from antiretroviral-naïve patients suggests that the combination of lamivudine and zidovudine delays the emergence of mutations conferring resistance to zidovudine. Combination therapy with lamivudine plus zidovudine did not prevent phenotypic resistance to lamivudine. However, phenotypic resistance to lamivudine did not limit the antiretroviral activity of combination therapy with lamivudine plus zidovudine. In antiretroviral therapy-naïve patients, phenotypic resistance to lamivudine emerged more

slowly on combination therapy than on lamivudine monotherapy. In the zidovudine-experienced patients on lamivudine plus zidovudine, no consistent pattern of changes in phenotypic resistance to lamivudine or zidovudine was observed.

Zidovudine
In vitro resistance to zidovudine is due to the accumulation of specific mutations in the HIV reverse transcriptase coding region. Five amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) have been described in viruses with decreased *in vitro* susceptibility to zidovudine inhibition. The extent of resistance appears to be correlated with number of mutations in reverse transcriptase.

Cross-Resistance
In vitro, isolates selected for resistance to abacavir may also be resistant to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. The M184V mutation has been shown to partially restore viral susceptibility to zidovudine.

The likelihood of a response to TRIZIVIR in an individual patient who has received prior treatment with other nucleoside analogues cannot be predicted. However, limited data seems to suggest patients with viral isolates carrying only the M184V mutation experienced comparable decreases in plasma HIV-1 RNA to patients with wild-type virus.

HIV isolates with multi-drug resistance to zidovudine, didanosine, zalcitabine, stavudine and lamivudine were recovered from a small number of patients treated for ≥ 1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→Leu, Phe116→Tyr and Gln151→Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine and stavudine.

Cytotoxicity
The results of cytotoxicity studies in various assays have shown little cytotoxic action with lamivudine. Cytotoxicity of lamivudine was compared with that of zidovudine, zalcitabine and didanosine in four T-lymphoblastoid cell lines; one monocyte/macrophage-like cell line; one B-lymphoblastoid cell line; and peripheral blood lymphocytes (PBLs) using both cell proliferation (CP) and [^{3}H]-thymidine uptake (Td) assays. In the CP assay, lamivudine was the least toxic of the four compounds. [^{3}H]-thymidine uptake results demonstrated a similar trend to those from the CP assays. Lamivudine had no cytotoxic effect when incubated for 10 days with phytohemagglutinin (PHA)-activated human lymphocytes or human macrophages.

The cytotoxicity of combinations of lamivudine with zidovudine, zalcitabine or didanosine was evaluated in PHA-activated PBLs and CEM cells by measuring cellular uptake of [^{3}H]-thymidine. Lamivudine greatly reduced the cytotoxicity of zalcitabine,

slightly reduced the cytotoxicity of zidovudine in some cases, and did not alter the cytotoxicity of didanosine.

In myelotoxicity studies *in vitro*, lamivudine demonstrated no toxic effects against erythroid, granulocyte-macrophage, pluripotent or stromal progenitor cells from healthy human donors. Lamivudine was not toxic to human hematopoietic supportive stroma, nonadherent hematopoietic cells, or stromal fibroblasts and produced minimal changes in cytokine (GM-CSF) production from mitogen-stimulated bone marrow stromal cells. Lamivudine was less toxic than zidovudine, zalcitabine, ara-C, 3FT and stavudine in these studies. In another study, lamivudine was not toxic to activated human T-cells.

The cytotoxicity of zidovudine for various cell lines was determined using a cell growth inhibition assay. ID_{50} values for several human cell lines showed little growth inhibition by zidovudine except at concentrations > 50 µg/mL. However, one human T-lymphocyte cell line was sensitive to the cytotoxic effect of zidovudine with an ID_{50} of 5 µg/mL. Moreover, in a colony-forming unit assay designed to assess the toxicity of zidovudine for human bone marrow, an ID_{50} value of < 1.25 µg/mL was estimated. Two of 10 human lymphocyte cultures tested were found to be sensitive to zidovudine at 5 µg/mL or less.

TOXICOLOGY

Acute Toxicity

Acute toxicity studies with abacavir, lamivudine and zidovudine have been performed in the mouse and rat.

Abacavir

Single oral or intravenous dose acute toxicity studies in the mouse and rat revealed no significant effects. The maximum non-lethal oral dose of abacavir in the mouse and rat was at least 100- and 115-fold greater, respectively, than the maximum intended therapeutic dose in humans of 300 mg b.i.d. (12 mg (base)/kg/day for a 50 kg person).

Lamivudine

The acute oral administration of very high doses of lamivudine (two doses of 2,000 mg/kg) in mice was associated with transient increases in sexual activity in males and general activity in males and females. There were no deaths and no evidence of target organ toxicity. Therefore the maximum non-lethal oral dose of lamivudine in mice is greater than two doses of 2,000 mg/kg.

The acute intravenous administration of lamivudine at 2,000 mg/kg was well tolerated by both mice and rats and was not associated with any target organ toxicity. A number of non-specific clinical signs were observed which were more severe in rats but were all of relatively short duration.

Zidovudine
Acute toxicity studies with zidovudine in mice and rats at doses up to 750 mg/kg produced only one death, in a mouse given 487 mg/kg of zidovudine. Death was preceded by chronic convulsions. Decreased activity, ptosis and laboured breathing were noted in other animals for up to 35 minutes post-dose. No effects were seen during the 14-day post-dose observation period.

In a second set of acute toxicity studies at higher doses of zidovudine, the median lethal doses for mice were 3,568 mg/kg and 3,062 mg/kg for male and female, respectively. In rats, the median lethal doses were 3,084 mg/kg for males and 3,683 mg/kg for females.

Clinical signs noted prior to death included ptosis, decreased activity, ataxia, body tremors, urine stains and prostration in mice. In rats, decreased activity and salivation occurred in most animals; the males receiving 5,000 mg/kg also exhibited rough coats and lacrimation.

Long-Term Toxicity

Abacavir
Repeated oral administration of abacavir succinate to mice at 330 mg/kg/day for up to 6 months, and to monkeys at 300 mg/kg/day for up to 52 weeks, or abacavir sulfate to rats at 530 mg/kg/day for up to 3 months, resulted in few changes which were mostly reversible.

The only consistent findings in rodents and monkeys were changes in the liver. Increases in liver weights seemed to be dose-related in the monkey. Slight increases in serum alanine aminotransferase and triglycerides were also observed in monkeys. Microscopically, slight centrilobular hepatocellular hypertrophy was seen in these animal species. In high dose monkeys, slightly swollen mitochondria, a decrease in the amount of rough endoplasmic reticulum and an increase in the number of lysosomes were observed using electron microscopy. Occasional individual cell necrosis, pigment deposits in centrilobular hepatocyte and Kupffer cells were seen in mice and rats. Additional changes observed in toxicity studies included slight alterations in cholesterol, albumin and/or total protein in mice and/or rats and transient reductions in hematology parameters in monkeys. Clinical observations of toxicity (including emesis, hunched posture, hypoactivity, decreased appetite, and abnormal feces) occurred in monkeys administered high doses of abacavir daily for 12 months.

Lamivudine
In repeat dose toxicity studies, lamivudine was very well tolerated in the rat at oral doses up to 2,000 mg/kg b.i.d. for 6 months. Treatment-related effects were restricted to minor hematological (mainly red cell parameters), clinical chemistry and urinalysis changes, and the mucosal hyperplasia of the cecum (in the 6 month study). The no (toxicologically important) effect level was 450 mg/kg b.i.d.

In the dog, oral doses of lamivudine 1,500 mg/kg b.i.d. in males and 1,000 mg/kg b.i.d. in females for a period of 12 months were well tolerated. Treatment related changes included reductions in red cell counts at all dose levels, associated with increased MCV and MCH, and reductions in total leucocyte, neutrophil and lymphocyte counts in high dose animals, but with no effect on bone marrow cytology. Deaths were seen in females dosed with 1,500 mg/kg b.i.d. in a 3 month study but not in a 12 month study, using a dose of 1,000 mg/kg b.i.d.

When administered orally for one month, at a dose of 1,000 mg/kg b.i.d., lamivudine demonstrated low hematotoxic potential in the mouse, and did not significantly enhance the hematotoxicity of zidovudine or interferon α.

Zidovudine

In repeat dose toxicity studies, zidovudine was well tolerated in rats at oral doses of up to 500 mg/kg/day for 13 weeks and 450mg/kg/day for 52 weeks. Treatment-related effects included increased blood glucose in females that received 500mg/kg/day for 13 weeks and moderate, reversible macrocytic anemia with reticulocytosis in rats that received 450 mg/kg/day for 52 weeks. Monkeys that received oral doses of up to 300mg/kg/day zidovudine for up to 52 weeks had dose related macrocytic anemia (decreased RBC, HCT and HB, increased MCV and MCH) which did not worsen from 26 to 52 weeks. After 4 weeks recovery, bone marrow smears were similar in control and treated animals. The severity of anemia was similar after 3, 6 and 12 months of treatment.

Carcinogenicity and Mutagenicity

Abacavir

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

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

Reductions in survival and body weight in rats at 600 mg/kg/day resulted in the early discontinuation of dosing in Weeks 84 (males) and 100 (females). Survival in mice was also reduced at 330 mg/kg/day, resulting in the early discontinuation of dosing of males in Week 98.

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

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

In an *in vitro* cytogenetic study performed in human lymphocytes, abacavir induced chromosomal aberrations following exposure at 2,800 and 3,200 μg/mL for 3 hours in the presence of metabolic activation and after exposure at 100 and 125 μg/mL for 50.3 hours in the absence of metabolic activation. The abacavir concentrations at which evidence of genotoxicity was seen *in vitro* were at least 33 times higher than the expected maximum human blood level.

In an *in vivo* mouse bone marrow micronucleus test, there was a small (2.3-fold) increase in the number of micronucleated polychromatic erythrocytes in males at 1,000 mg/kg. No significant increase was seen in bone marrow harvested from females. Findings in the micronucleus test were seen at systemic exposures (in terms of AUC) approximately nine times higher than exposure in humans at the therapeutic dose, and C_{max} values approximately 14 times higher than the maximum concentration in humans at the therapeutic dose.

No evidence of mutagenicity (with or without metabolic activation) was observed in bacterial mutagenicity assays at concentrations up to approximately 5,000 μg/plate. In a mutagenicity assay conducted in L5178Y mouse lymphoma cells, abacavir was weakly mutagenic following exposure at 250 μg/mL for 24 hours in the absence of metabolic activation. Abacavir was not mutagenic to L5178Y mouse lymphoma cells in a 3 hour exposure in the presence or absence of metabolic activation.

Lamivudine
Traditional 24 month carcinogenicity studies using lamivudine have been conducted in mice and rats at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at recommended therapeutic doses. The following results should be noted. In mice, there appeared to be an increased incidence of histiocytic sarcoma in female mice treated with 180 mg/kg/day (6 of 60 mice) and 2,000 mg/kg/day (5 of 60 mice) when compared to control mice (two control groups with 1 of 60 and 2 of 60 mice). There did not appear to be an increased incidence in histiocytic sarcoma in female mice treated with 600 mg/kg/day (3 of 60 mice). It should be noted that the control incidence of this type of tumour in this strain of mice can be as high as 10% similar to that found in the 180 and 2,000 mg/kg/day groups. In rats, there appeared to be an increased incidence of endometrial epithelial tumours in female rats treated with 3,000 mg/kg/day (5 of 55 rats) when compared to control rats (two control groups each with 2 of 55 rats). There did not appear to be an increased incidence for endometrial tumours in rats treated with 1,000 mg/kg/day (2 of 55 rats) or 300 mg/kg/day (1 of 55 rats). It should be noted that there did not appear to be an increased incidence of any proliferative, non-neoplastic, epithelial lesions in treated female rats when compared to control rats, and the incidence of adenocarcinoma (5/55 or 9%) was only slightly higher than recorded controls at the

laboratory where the study was conducted (4/50 or 8%). The statistical significance of the findings in mice and rats varied with the statistical analysis conducted, and therefore, the statistical and hence, the clinical significance of these findings are uncertain. However, based on the similarity to historical control data, it was concluded that the results of long term carcinogenicity studies in mice and rats for lamivudine did not seem to show a carcinogenic potential relevant for humans.

Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg (approximately 65 times the recommended human dose based on body surface area comparisons).

Zidovudine
Zidovudine was administered orally at three dosage levels to separate groups of mice and rats (60 females and 60 males in each group). Initial single daily doses were 30, 60 and 120 mg/kg/day in mice and 80, 220 and 600 mg/kg/day in rats. The doses in mice were reduced to 20, 30 and 40 mg/kg/day after day 90 because of treatment-related anemia, whereas in rats only the high dose was reduced to 450 mg/kg/day on day 91 and then to 300 mg/kg/day on day 279.

In mice, seven late-appearing (after 19 months) vaginal neoplasms (five non-metastasizing squamous cell carcinomas, one squamous cell papilloma, and one squamous polyp) occurred in animals given the highest dose. One late-appearing squamous cell papilloma occurred in the vagina of a middle dose animal. No vaginal tumours were found at the lowest dose.

In rats, two late-appearing (after 20 months), non-metastasizing vaginal squamous cell carcinomas occurred in animals given the highest dose. No vaginal tumours occurred at the low or middle dose in rats. No other drug-related tumours were observed in either sex of either species.

At doses that produced tumours in mice and rats, the estimated drug exposure (as measured by AUC) was approximately 8 times (mouse) and 57 times (rat) the estimated human exposure following a single dose of 300 mg.

Two transplacental carcinogenicity studies were conducted in mice. One study administered zidovudine at doses of 20 mg/kg/day or 40 mg/kg/day from gestation day 10 through parturition and lactation with dosing continuing in offspring for 24 months postnatally. The doses of zidovudine employed in this study produced zidovudine exposures approximately three times the estimated human exposure at recommended doses. After 24 months, an increase in incidence of vaginal tumours was noted with no increase in tumours in the liver or lung or any other organ in either gender. These findings are consistent with results of the standard oral carcinogenicity study in mice, as

described earlier. A second study administered zidovudine at maximum tolerated doses of 12.5 mg/day or 25 mg/day (~1,000 mg/kg nonpregnant body weight or ~450 mg/kg of term body weight) to pregnant mice from days 12 through 18 of gestation. There was an increase in the number of tumours in the lung, liver and female reproductive tracts in the offspring of mice receiving the higher dose level of zidovudine. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

No evidence of mutagenicity (with or without metabolic activation) was observed in the Ames *Salmonella* mutagenicity assay at concentrations up to 10 μg per plate, which was the maximum concentration that could be tested because of the antimicrobial activity of zidovudine against the *Salmonella* species. In a mutagenicity assay conducted in L5178Y/$TK^{+/-}$ mouse lymphoma cells, zidovudine was weakly mutagenic in the absence of metabolic activation only at the highest concentrations tested (4,000 and 5,000 μg/mL). In the presence of metabolic activation, the drug was weakly mutagenic at concentrations of 1,000 μg/mL and higher. In an *in vitro* mammalian cell transformation assay, zidovudine was positive at concentrations of 0.5 μg/mL and higher. In an *in vitro* cytogenetic study performed in cultured human lymphocytes, zidovudine induced dose-related structural chromosomal abnormalities at concentrations of 3 μg/mL and higher. No such effects were noted at the two lowest concentrations tested, 0.3 and 1 μg/mL. In an *in vivo* cytogenetic study in rats given a single intravenous injection of zidovudine at doses of 37.5 to 300 mg/kg, there were no treatment-related structural or numerical chromosomal alterations in spite of plasma levels that were as high as 453 μg/mL 5 minutes after dosing.

In two *in vivo* micronucleus studies (designed to measure chromosome breakage or mitotic spindle apparatus damage) in male mice, oral doses of zidovudine 100 to 1,000 mg/kg/day administered once daily for approximately 4 weeks induced dose-related increases in micronucleated erythrocytes. Similar results were also seen after 4 or 7 days of dosing at 500 mg/kg/day in rats and mice.

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.

In a study involving 11 AIDS patients, it was reported that the seven patients who were receiving zidovudine (1,200 mg/day) as their only medication for 4 weeks to 7 months showed a chromosome breakage frequency of 8.29 ± 2.65 breaks per 100 peripheral lymphocytes. This was significantly ($p < 0.05$) higher than the incidence of 0.5 ± 0.29 breaks per 100 cells that was observed in the four AIDS patients who had not received zidovudine.

Reproduction and Teratology

Abacavir

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at doses of up to 500 mg/kg/day.

Reproduction studies were performed in rats and rabbits at orally administered doses up to 1,000 mg/kg/day and 700 mg/kg/day, respectively. These doses in rats and rabbits achieved approximately 35 and 8.5 times, respectively, the exposure associated with the recommended human dose. In the rat, development toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed at the highest dose assessed. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg/day, a dose that was toxic to the parental generation. This dose in rats achieved approximately 33 times the exposure with the usual human dose. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations, at doses up to 700 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC). The offspring of female rats treated with abacavir at 500 mg/kg (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life.

Lamivudine

A range of studies has been performed to assess the effects of repeated oral administration of lamivudine upon mammalian reproduction and development.

In a rat fertility study, except for a few minor changes in high dose (2,000 mg/kg b.i.d.) animals, the overall reproductive performance of the F_0 and F_1 generation animals, and the development of the F_1 and F_2 generation, was unaffected by treatment with lamivudine.

Lamivudine was not teratogenic in the rat or rabbit, at doses up to 2,000 mg/kg b.i.d. and 500 mg/kg b.i.d., respectively. In the rabbit a slight increase in the incidence of pre-implantation loss at doses 20 mg/kg b.i.d. and above indicates a possible early embryolethal effect. There was no such effect in the rat. These marginal effects occurred at relatively low doses, which produced plasma levels comparable to those achieved in patients.

In a peri-/post-natal/juvenile toxicity study in rats, some histological inflammatory changes at the ano-rectal junction and slight diffuse epithelial hyperplasia of the cecum were observed in dams and pups at the high dose level. An increased incidence of urination upon handling was also seen in some offspring receiving 450 or 2,000 mg/kg. In addition, a reduction in testes weight was observed in juvenile males at 2,000 mg/kg which was associated with slight to moderate dilatation of the seminiferous tubules.

Zidovudine
In an *in vitro* experiment with fertilized mouse oocytes, zidovudine exposure resulted in a dose-dependent reduction in blastocyst formation.

No effect on male or female fertility (judged by conception rates) was seen in rats given zidovudine orally at doses up to 450 mg/kg/day.

In a fertility and reproduction study, male rats were dosed for 85 days prior to mating and females for 26 days prior to mating and throughout gestation and lactation. No fetal malformations or variations occurred, but the mid- and high-doses were both embryotoxic, increasing the number of early resorptions and decreasing litter sizes. No embryotoxic effects occurred in untreated females mated with treated males.

No evidence of teratogenicity was found in rats given oral doses of zidovudine of up to 500 mg/kg/day on days 6 through 15 of gestation. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one-half of the daily dose) in rats of 66 to 226 times the peak human plasma concentrations.

In a second teratology study in rats, an oral dose of 3,000 mg/kg/day (very near the oral median lethal dose in rats of 3683 mg/kg/day) caused marked maternal toxicity and an increase in the incidence of fetal malformations including absent tail, anal atresia, fetal edema, situs inversus, diaphragmatic hernia, bent limb bones, atlas occipital defect and vertebral and/or rib anomalies. There was also a significant increase in the number of litters with bent ribs, reduced ossification of the vertebral arches and presacral vertebrae. This dose resulted in peak zidovudine plasma concentrations 117 times peak human plasma concentrations. (Estimated area-under-the-curve AUC in rats at this dose level was 327 times the daily AUC in humans following a single dose of 300 mg). No evidence of teratogenicity was seen in the experiment at doses of 600 mg/kg/day or less.

In one of two studies in pregnant rabbits, the incidence of fetal resorptions was increased in rabbits given 500 mg/kg/day. There was no evidence of a teratogenic effect at any dose level. The doses used in these studies resulted in peak zidovudine plasma concentrations in rabbits of 5 to 49 times mean peak human plasma concentrations achieved following a single 300 mg dose of zidovudine.

A separate peri- and post-natal study was conducted in pregnant rats given doses of 0, 50, 150 and 450 mg/kg/day (0, 25, 75 or 225 bid) from day 17 of gestation through to day 21 of lactation. There were no adverse effects noted in either generation. The reproductive capacity of those F_1 generation pups which were raised to sexual maturity was not affected.

Neonatal animals were given 0, 80, 250 or 750 mg/kg/day for two months, starting on lactation day 8. Treatment-related alterations occurred only in the high-dose group and were reversible macrocytic anemia and increased urine output in both sexes, and decreased body weight gain in males. Mild to moderate increases in spleen weights were also noted.

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PART III: CONSUMER INFORMATION

PrTRIZIVIR
abacavir (as abacavir sulfate)/lamivudine/zidovudine

This leaflet is part III of a three-part "Product Monograph" published for TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) approved for sale in Canada and is designed specifically for Consumers. Please read this leaflet carefully before you start to take your medicine. You may need to read this leaflet again during your treatment. This leaflet is a summary and will not tell you everything about TRIZIVIR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
The Human Immunodeficiency Virus (HIV) is a retrovirus (a type of virus). Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

TRIZIVIR belongs to a group of antiretroviral medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs), and is used in combination with other antiretrovirals to treat Human Immunodeficiency Virus (HIV) infection.

What it does:
TRIZIVIR does not cure HIV, but helps to prevent further damage to the immune system by slowing down production of new viruses. You must be sure to be seen regularly by your health care provider.

TRIZIVIR also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body fight infection.

When it should not be used:
TRIZIVIR should not be taken if:

- you previously had an allergic reaction (hypersensitivity) to the active ingredient abacavir, which is also included in medicines called ZIAGEN, KIVEXA and TRIUMEQ (see **What the important nonmedicinal ingredients are**).
- you previously had an allergic reaction to the active ingredient lamivudine which is included in medicines called 3TC, COMBIVIR or KIVEXA or zidovudine which is included in a medicine called RETROVIR or any of the other ingredients found in TRIZIVIR (see **What the important nonmedicinal ingredients are**).
- you have liver disease.
- you have a very low red blood cell count (anemia) or very low white blood cell count (neutropenia).

What the medicinal ingredient is:
TRIZIVIR is a treatment that contains a fixed dose combination of three active ingredients that are currently available as separate medicines: ZIAGEN (abacavir sulfate), 3TC (lamivudine) and RETROVIR (zidovudine). Each TRIZIVIR tablet contains 300 mg abacavir, 150 mg of lamivudine and 300 mg zidovudine.

What the important nonmedicinal ingredients are:
Each TRIZIVIR tablet contains the following nonmedicinal ingredients: hydroxypropyl methyl cellulose, indigotine aluminum lake, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

What dosage forms it comes in:
TRIZIVIR tablets are blue/green, capsule-shaped, film-coated tablets imprinted with GX LL1 on one face, containing 300 mg abacavir as abacavir sulfate, 150 mg lamivudine and 300 mg zidovudine. Available in bottles of 60.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reaction
You should be screened for the HLA-B*5701 gene variation prior to starting or re-starting treatment with TRIZIVIR. Patients who have the HLA-B*5701 gene variation have a high risk of developing a hypersensitivity reaction (serious allergic reaction) to abacavir, which is in the drug TRIZIVIR. This hypersensitivity reaction **can be life threatening** if you continue to take TRIZIVIR (see **Important Information on Hypersensitivity Reactions**).

Build-up of acid in your blood (lactic acidosis) and swollen and fatty liver:
Lactic acidosis (too much acid in the blood) and swollen and fatty liver (hepatomegaly with steatosis), including fatal cases, have been reported using nucleoside analogues alone or in combination. If you suffer symptoms (See Serious Side Effects Table), contact your doctor.

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

Important Information on Hypersensitivity Reactions
If you get two or more of the following groups of symptoms while taking TRIZIVIR contact your doctor immediately to find out if you should stop taking TRIZIVIR:

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

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

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

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

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

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

Before you use TRIZIVIR, talk to your doctor or pharmacist:

- About all your medicines and medical conditions
- If you have kidney or liver disease (including hepatitis B or C)
- If you are taking interferon or ribavirin
- If you have had previous use of any NRTI class medicine
- If you have been tested and know whether or not you have a gene variation called HLA-B*5701
- If you are pregnant, or planning to become pregnant, breastfeeding or planning to breastfeed
- About all the medicines you are taking including vitamins, herbal supplements and nonprescription drugs

Other Special Warnings

Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

The class of medicines to which TRIZIVIR belongs (NRTIs), can cause a condition called lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. Symptoms of lactic acidosis include feeling of weakness, loss of appetite, sudden unexplained weight loss, upset stomach and difficulty breathing or rapid breathing. This rare but serious side effect occurs more often in women. If you have liver disease you may also be more at risk of getting this condition. While you are being treated with TRIZIVIR, your doctor will monitor you closely for any signs that you may be developing lactic acidosis.

Zidovudine, one of the three active ingredients in TRIZIVIR, may also cause a decrease in certain types of blood counts (including red blood cells, white blood cells and platelets) and an increase in certain liver enzymes.

Zidovudine can affect the production of red blood cells, resulting in anemia. If this happens, the symptoms are tiredness and shortness of breath. Less commonly, the production of a certain type of white blood cell may be reduced which can make you more prone to infections. Your doctor may want you to have a blood test from time to time to check the blood cell count.

If you have a hepatitis B infection, you should not stop TRIZIVIR without instructions from your doctor, as you may have a recurrence of your hepatitis. This may occur due to suddenly stopping the active ingredient lamivudine in TRIZIVIR.

Some HIV medicines including abacavir may increase your risk of heart attack. If you have heart problems, smoke or suffer from diseases that increase your risk of heart disease such as high blood pressure and diabetes, tell your doctor. Do not stop taking your medication unless you are advised to do so by your doctor.

You may continue to develop other infections and other illnesses associated with HIV disease. You should therefore keep in regular contact with your doctor while taking TRIZIVIR.

TRIZIVIR helps to control your condition but is not a cure for HIV infection. You will need to take it every day.

Unless you suspect you are having an allergic reaction with TRIZIVIR, do not stop taking your medicine without first talking to your doctor.

Treatment with TRIZIVIR has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You should continue to use appropriate precautions to prevent this.

Use of this medicine during pregnancy and breastfeeding:
If you are pregnant, or planning to become pregnant soon, you must inform your doctor before taking any medicine. The safe use of TRIZIVIR in pregnancy has not been established. Your doctor will decide whether you should continue to be treated with TRIZIVIR if you are pregnant. If you take TRIZIVIR while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.

Babies and infants exposed to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) during pregnancy or labour show minor temporary increases in blood levels of lactate. The clinical importance of these temporary increases is unknown.

These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies. There have been very rare reports of disease that affect the neonatal (babies) nervous system such as delayed development and seizures. The long term effects of TRIZIVIR are not known.

It is recommended that HIV infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV from mother to child. All three of the active substances in TRIZIVIR are likely to be found in breast milk.

You are recommended **not** to breastfeed your baby while taking TRIZIVIR.

Remember: This medicine is for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

INTERACTIONS WITH THIS MEDICATION

Some drugs may change the usefulness and safety of TRIZIVIR. It is important that your doctor knows about all your medicines so that you get the best possible treatment. Tell your doctor about all your medicines, including vitamin supplements, herbal remedies or homeopathic remedies, including those you have bought yourself.

TRIZIVIR should not be taken with stavudine or emtricitabine.

It is important to tell your doctor or pharmacist about all the medicines listed below or any that you are taking or have recently taken, including those you have bought yourself:

- Phenytoin, valproic acid, oxazepam, lorazepam
- Acetylsalicylic acid
- Codeine, morphine, methadone, rifampicin, indomethacine, ketoprofen, naproxen, cimetidine, clofibrate, Isoprinosine, probenecid
- Pentamine, pyrimethamine, co-trimoxazole, dapsone, atovaquone, amphotericin, flucytosine, interferon
- Vincristine, vinblastine, adriamycin and doxorubicin
- Clarithromycin
- Fluconazole
- Ganciclovir
- Retinoids
- Methadone
- Trimethoprim sulphamethoxazole (co-trimoxazole)
- Interferon and/or ribavirin
- Sorbitol-containing medicines (usually liquids) used regularly

If you are taking methadone, your doctor may need to adjust your methadone dose, as abacavir increases the rate at which methadone leaves your body. This is unlikely to affect most methadone users.

In men, alcohol does increase the amount of abacavir in your blood. However, the meaning of this is unknown. This interaction had not been studied in women.

PROPER USE OF THIS MEDICATION

Usual dose:
Take TRIZIVIR **exactly as your doctor has advised you, and try not to miss any doses**. The usual dose is one tablet twice a day. Swallow the tablet whole with water. TRIZIVIR can be taken with or without food. TRIZIVIR is a set (fixed) dose combination of abacavir sulfate, lamivudine and zidovudine and therefore cannot be dose-reduced. If you have kidney or liver problems or if you weigh less than 40 kg, then your medicine may be changed to the separate medicines, ZIAGEN, 3TC and RETROVIR (AZT). If you are unsure about how to take it, ask your doctor or pharmacist. The use of TRIZIVIR has not been established in patients less than 18 years of age, and in elderly patients (> 65 years).

If you are also taking clarithromycin, your doctor may advise you to take this medication at least 2 hours before or 2 hours after TRIZIVIR, to avoid a drug interaction.

Overdose:

If you are concerned that you may have taken too much TRIZIVIR, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
It is important to take this medicine as prescribed to ensure you get maximum benefit. If you forget to take a dose, take it as soon as you remember, and then continue as before. Do not take a double dose to make up for forgotten individual doses.

If you stopped taking TRIZIVIR:
If you stop taking TRIZIVIR because of side effects or illness, you must contact your doctor before restarting to make sure that symptoms of a hypersensitivity reaction have not been missed. In some cases your doctor will ask you to restart TRIZIVIR under direct medical supervision or in a place where you will be able to get ready access to medical care if needed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TRIZIVIR can have side effects. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by TRIZIVIR, by other medicines you are taking at the same time or by the HIV infection. For this reason it is very important that you inform your doctor about any changes in your health.

A hypersensitivity reaction (serious allergic reaction) has been reported in patients who have been treated with abacavir. This is described in the section on Hypersensitivity Reaction (under WARNINGS AND PRECAUTIONS) in the beginning of this leaflet. It is important that you read and understand the information about this serious reaction.

TRIZIVIR contains three active ingredients. Therefore, all side effects that have been reported in patients taking these medicines separately may also occur in patients taking TRIZIVIR. The most common side effects reported for these active ingredients (abacavir, lamivudine and zidovudine) are in bold text:

- **Nausea, vomiting, stomach pain, diarrhea, loss of appetite**, flatulence and indigestion.
- **Headache**, dizziness, numbness, tingling sensation or sensation of weakness in the limbs, convulsions (fits), **difficultly sleeping**, tiredness, anxiety, depression, general feeling of being unwell.
- Cough, breathlessness.
- Disease of heart muscle (cardiomyopathy)
- Joint pain, **muscle pain and inflammation**, including rare reports of breakdown of muscle tissue.
- **Fatigue, fever, malaise and lethargy**. Taste changes, chills, urinary frequency, enlargement of the breasts in men, chest pain, flu-like symptoms.
- Nail and skin colour changes, patchy colour changes in the mouth, **rash**, very rare reports of serious skin reactions, itching, sweating and **hair loss**.
- Liver disorders such as an enlarged liver, fatty liver and jaundice. Temporary increases in certain substance (enzymes) produced by the liver. Inflammation of the pancreas.
- Anemia (low red blood cell count) and neutropenia/leucopenia (low white blood cell count) have been reported. If the production of red blood cells is reduced you may have symptoms of tiredness or breathlessness. A reduction in your white blood cell count can make you more prone to infection.
- Reduction in platelets (blood cells important for blood clotting) has been reported. If you have a low platelet count you may notice that you bruise more easily.

Treatment with TRIZIVIR or other medicines that contain zidovudine may cause a loss of fat from legs, arms and face (lipoatrophy). Your doctor should monitor for signs of lipoatrophy. Tell your doctor if you notice any loss of fat from your legs, arms, and face. When these signs occur, your doctor will assess if TRIZIVIR should be stopped and your HIV treatment changed. If you stop taking TRIZIVIR, it may take several months to see any lost fat return. You may not regain all of your lost body fat.

Changes to your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

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

- High temperature (fever), redness, rash or swelling
- Fatigue

- Joint or muscle pain
- Numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
- Palpitations (chest pain) or rapid heart rate
- Yellowing of the eyes and skin

If you notice these or any symptoms of inflammation or infection, tell your doctor immediately.

Inflammation in the pancreas (pancreatitis) has been observed in patients treated with abacavir, lamivudine and zidovudine, although it was not clear whether this was due to the medicine or the HIV infection itself (See Side Serious Side Effects table). If your doctor detects clinical signs, symptoms or lab tests suggestive of pancreatitis, they will stop treatment with TRIZIVIR immediately.

Always tell your doctor or pharmacist if any of the side effects mentioned becomes severe or troublesome, or if you notice any other side effects not listed in this leaflet.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Hypersensitivity to abacavir: Serious allergic reaction and 2 or more of the following symptoms: fever, skin rash, nausea, vomiting, diarrhea, abdominal pain, severe tiredness, achiness, general ill-feeling, sore throat, shortness of breath.		**X**	
Uncommon	Blood problems and symptoms such as anemia (lowered red blood cell count – resulting in fatigue, breathlessness), low white blood cell count (neutropenia – increasing chance of infection) reduced platelets (blood cells important for blood clotting – could increase chance of bruising) and increases in enzymes produced by the liver.		**X**	
Rare	Pancreatitis (inflammation of the pancreas) and symptoms such as nausea, vomiting, and abdominal pain.		**X**	
	Lactic acidosis (high level of acid in the blood): Weight loss, fatigue, malaise, abdominal pain, shortness of breath, severe hepatomegaly (swollen and enlarged liver) with symptoms of liver problems such as nausea, vomiting, abdominal pain, weakness and diarrhea.		**X**	

HOW TO STORE IT

Store between 15º and 30ºC.

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

Do not take your medicine after the expiry date shown on the bottle and the carton.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.viivhealthcare.com
or by contacting the sponsor, ViiV Healthcare ULC at:
245 Boulevard Armand-Frappier
Laval, Quebec
H7V A47
1-877-393-8448

This leaflet was prepared by ViiV Healthcare ULC.

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INFORMATION FOR PRESCRIBERS:

A copy of the warning card included with the TRIZIVIR carton is shown below.

WARNING CARD

TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) Tablets

Patients taking TRIZIVIR (abacavir sulfate/lamivudine/zidovudine) may develop a hypersensitivity reaction (a serious allergic reaction) which can be life-threatening if you continue to take TRIZIVIR. **If you notice two or more of the following sets of symptoms while taking TRIZIVIR, contact your doctor immediately to find out if you should stop taking TRIZIVIR.**

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

If you have already had this reaction to **TRIZIVIR**, **never take any medicine containing abacavir, such as ZIAGEN** (abacavir sulfate), **KIVEXA** (abacavir sulfate/lamivudine) **or TRIUMEQ** (dolutegravir/ abacavir/lamivudine) **again**. **If you take any medicine containing abacavir, such as TRIZIVIR, KIVEXA, ZIAGEN or TRIUMEQ again, within hours you may experience a life-threatening lowering of your blood pressure or death.**

Carry this card with you at all times.

You should return all of your unused TRIZIVIR to your doctor or pharmacist for proper disposal.

ViiV Healthcare ULC
Laval, Quebec H7V 4A7