

PRODUCT MONOGRAPH

Pr **TRIZIVIR**[®]

(abacavir sulfate/lamivudine/zidovudine)

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

Antiretroviral Agent

ViiV Healthcare Shire Canada
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Mississauga, Ontario
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PrTRIZIVIR®

abacavir sulfate/lamivudine/zidovudine

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|---|---|
| Oral | Tablet/300 mg abacavir, 150 mg lamivudine and 300 mg zidovudine | None |

For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

INDICATIONS AND CLINICAL USE

TRIZIVIR® (abacavir sulfate/lamivudine/zidovudine) is indicated for:

- the treatment of Human Immunodeficiency Virus (HIV) infection in adult patients. This fixed-dose combination is a simplified dosing alternative to the three components used separately in similar dosages.

This indication is supported by the results obtained in controlled clinical trials with the separate components (abacavir sulfate, lamivudine and zidovudine). The demonstration of benefit of this combination is mainly based on results of studies of antiretroviral naïve patients. In patients with high viral load (> 100,000 copies/mL) choice of therapy needs special consideration (see DETAILED PHARMACOLOGY: Clinical Trials section).

TRIZIVIR® was approved on pharmacokinetic and safety data only.

CONTRAINDICATIONS

- TRIZIVIR[®] (abacavir sulfate/lamivudine/zidovudine) is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the product (see DOSAGE FORMS, COMPOSITION AND PACKAGING section).
- TRIZIVIR[®] is contraindicated in patients with end stage renal disease.
- Due to the active ingredient abacavir, TRIZIVIR[®] is contraindicated in patients with hepatic impairment.
- Due to the active ingredient zidovudine, TRIZIVIR[®] is contraindicated in patients with abnormally low neutrophil counts ($< 0.75 \times 10^9/L$) or abnormally low hemoglobin levels (< 7.5 g/dL or 4.65 mmol/L).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Fatal Hypersensitivity Reactions**

Fatal hypersensitivity reactions have been associated with therapy with abacavir sulfate and other abacavir containing products. Therapy with TRIZIVIR[®] (abacavir sulfate/lamivudine/zidovudine) should be discontinued in patients developing signs or symptoms of hypersensitivity in 2 or more of the following groups: 1) fever, 2) rash, 3) gastrointestinal (including nausea, vomiting, diarrhea or abdominal pain), 4) constitutional (including generalized malaise, fatigue or achiness), 5) respiratory (including pharyngitis, dyspnea, cough and abnormal chest x-ray findings, predominantly infiltrates, which can be localized) (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions to Abacavir). To minimize the risk of a life threatening hypersensitivity reaction, TRIZIVIR[®] should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (acute onset of respiratory diseases, gastroenteritis or reactions to other medications).

The symptoms of a hypersensitivity reaction can occur at any time during treatment with abacavir, but usually occur within the first six weeks of therapy. **TRIZIVIR[®] or any other medicinal product containing abacavir (e.g. ZIAGEN[®], KIVEXA[®]) must never be restarted following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.** Severe or fatal hypersensitivity reactions can occur within hours after TRIZIVIR[®] re-introduction in patients who have no identified history or undiagnosed symptoms of hypersensitivity during their initial period of use of TRIZIVIR[®].

Patients who carry the HLA-B*5701 allele are at a significant increased risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, it is recommended that screening for HLA-B*5701 status be undertaken. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. Use of abacavir in patients known to carry the HLA-B*5701 allele is not recommended.

Cases of abacavir hypersensitivity have occurred in patients who are HLA-B*5701 negative. The clinical diagnosis of suspected hypersensitivity to abacavir remains the basis for clinical decision making in all patients. Therefore, it is important to permanently discontinue abacavir and not rechallenge with abacavir if hypersensitivity cannot be ruled out, regardless of the presence or absence of the HLA-B*5701 allele due to the potential for a severe or even fatal reaction (see WARNINGS and PRECAUTIONS: Hypersensitivity Reaction: Risk Factors: HLA-B*5701 Allele).

- **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. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. 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 or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations) (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

- **Post-Treatment Exacerbation of Hepatitis**

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. TRIZIVIR[®] is not indicated for the treatment of chronic HBV infection and the safety and efficacy of TRIZIVIR[®] have not been established in patients coinfecting with HBV and HIV. Exacerbations of hepatitis B have been reported in patients after the discontinuation of antiretroviral therapy. Patients coinfecting with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with TRIZIVIR[®] (see ADVERSE EVENTS, Post-Market Adverse Drug Reactions).

- **Pancreatitis**

Pancreatitis has been observed in some patients receiving abacavir and lamivudine. 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).

- **Pancreatitis in Pediatric Patients**

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, lamivudine containing products should be used with caution. Treatment with lamivudine containing products should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

General

TRIZIVIR[®] is a fixed dose combination of abacavir sulfate, lamivudine and zidovudine. TRIZIVIR[®] should not be administered concomitantly with either abacavir, lamivudine or zidovudine. The complete prescribing information for all agents being considered for use with TRIZIVIR[®] should be consulted before combination therapy with TRIZIVIR[®] is initiated.

The incidence of adverse reactions appears to increase with disease progression and patients should be monitored carefully, especially as disease progression occurs.

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions have been associated with therapy with abacavir sulfate, one of the three active ingredients of TRIZIVIR[®]. Patients who carry the HLA-B*5701 allele are at a significantly increased risk for experiencing a hypersensitivity reaction to abacavir. Other less common signs or symptoms of hypersensitivity include fever, skin rash, fatigue, myolysis, edema, paresthesia, anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions, gastrointestinal symptoms, such as nausea, vomiting, diarrhea or abdominal pain, and respiratory signs and symptoms such as pharyngitis, dyspnea, cough and abnormal chest x-ray findings predominantly infiltrates, which can be localized.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

The diagnosis of a hypersensitivity reaction should be carefully considered for patients presenting with symptoms of acute onset respiratory diseases, even if alternative respiratory diagnoses (pneumonia, bronchitis, pharyngitis or flu-like illness) are possible. **TRIZIVIR[®] or any other medicinal product containing abacavir must never be restarted following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life threatening hypotension and death.**

To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, TRIZIVIR[®] should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). TRIZIVIR[®] or any other medicinal product containing abacavir should not be re-started, even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

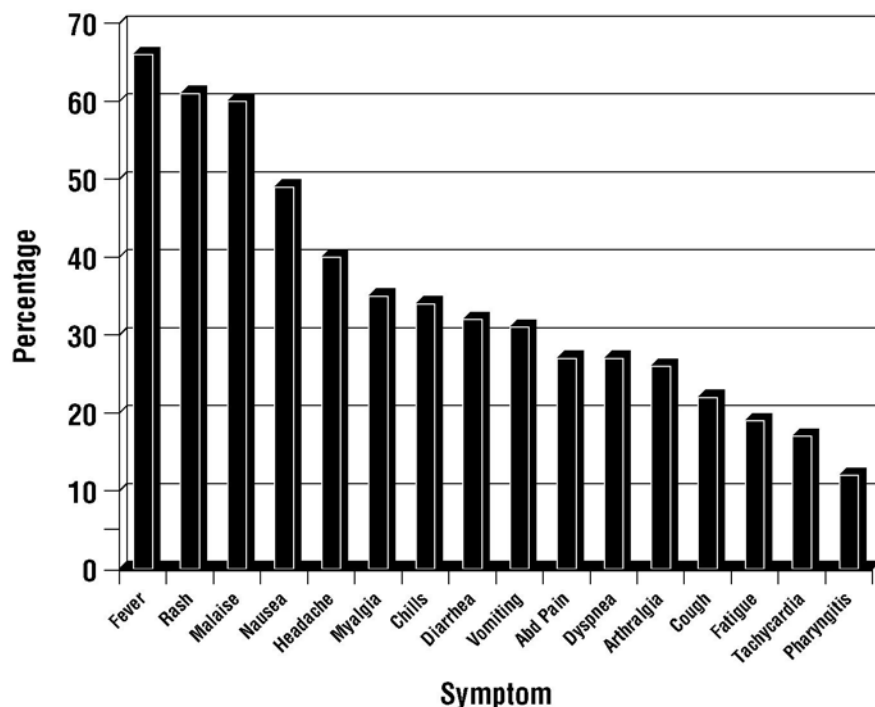
Severe or fatal hypersensitivity reactions can occur within hours after TRIZIVIR[®] re-introduction in patients who have no identified history or unrecognized symptoms of hypersensitivity during their initial period of use of TRIZIVIR[®].

Regardless of a patient's HLA-B*5701 status, if therapy with TRIZIVIR[®] or any other medicinal product containing abacavir has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If a hypersensitivity reaction cannot be ruled out, TRIZIVIR[®], or any other medicinal product containing abacavir (e.g. ZIAGEN[®], KIVEXA[®]) should not be restarted.**

If symptoms consistent with 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 and that reintroduction of TRIZIVIR[®] or introduction of any other abacavir containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

Overall, in clinical trials conducted before the introduction of screening for the HLA-B*5701 allele, hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n=206) in 9 clinical trials (range: 2% to 9%) with enrolment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. This reaction is characterised by the appearance of symptoms indicating multi-organ/body-system involvement. Symptoms can occur at any time during therapy, however they usually appear within the first 6 weeks (median time to onset 11 days) of initiation of treatment with TRIZIVIR[®] (see ADVERSE REACTIONS section).

Figure 1 Hypersensitivity Related Symptoms Reported with $\geq 10\%$ Frequency in Clinical Trials (n = 206 Patients)



A warning card with information for the patient about this hypersensitivity reaction is included in the TRIZIVIR[®] pack (see CONSUMER INFORMATION: Warning Card).

Risk Factors: HLA-B*5701 Allele:

Studies have shown that carriage of the HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. CNA106030 (PREDICT-1), a randomized, double blind study, evaluated the clinical utility of prospective HLA-B*5701 screening on the incidence of abacavir hypersensitivity reaction in abacavir-naïve HIV-1 infected adults (n = 1,650). In this study, use of pre-therapy screening for the HLA-B*5701 allele and exclusion of subjects with this allele reduced the incidence of clinically suspected abacavir hypersensitivity reactions from 7.8% (66/847) to 3.4% (27/803) ($p < 0.0001$). Based on this study, it is estimated that 61% of patients with the HLA-B*5701 allele will develop a clinically suspected hypersensitivity reaction during the course of abacavir treatment compared with 4% of patients who do not have the HLA-B*5701 allele.

Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment with abacavir. Screening is also recommended prior to re-initiating abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. For HLA-B*5701-positive patients, initiating or re-initiating treatment with an abacavir containing regimen is not recommended and should be considered only with close medical supervision and under exceptional circumstances where potential benefit outweighs the risk.

Skin patch testing is used as a research tool and should not be used to aid in the clinical diagnosis of abacavir hypersensitivity.

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

Carcinogenesis and Mutagenesis

Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay.

At systemic exposures approximately nine times higher than that in humans at the therapeutic dose, abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation (see TOXICOLOGY: Mutagenicity section).

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 subcutis of female rats. The majority of these tumours occurred at the highest abacavir dose in mice and rats, which correspond to 24 - 32 times the expected systemic exposure in humans (see TOXICOLOGY: Carcinogenicity section).

Cardiovascular

The results of a prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy (N=33,347) suggest that current or recent use (within the past 6 months) of abacavir may be associated with a potential increased risk of myocardial infarction. This elevated risk does not appear to increase further over time, and no excess risk was present in patients who had stopped taking abacavir more than 6 months previously. The relative risk of myocardial infarction was estimated to be 1.9 (95% CI 1.47-2.45). The absolute myocardial infarction rate was 6.1/1000 patient years of exposure for those recently exposed to abacavir compared to an absolute myocardial infarction rate of 2.6/1000 patient years of exposure for those not recently exposed. In addition, the absolute myocardial infarction rate ranged from 3.4 to 3.7/1000 patient years of exposure for patients recently exposed to other NRTIs (i.e. zidovudine, stavudine and lamivudine).

In a pooled analysis of GSK sponsored clinical trials (N=9639), no increased risk of myocardial infarction was observed with abacavir use. At this time, though the available data do not allow a definitive conclusion regarding the association between the use of abacavir and an increased risk of myocardial infarction, it is recommended that physicians discuss the potential benefits and risks of abacavir with their patients.

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

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (“buffalo hump”), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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/mm³ 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 section). 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 $1.0 \times 10^9/l$ (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 generalized weakness, anorexia, and sudden unexplained weight loss, gastrointestinal symptoms and respiratory symptoms (dyspnea and tachypnea).

Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering TRIZIVIR[®] to any patient 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 or hepatotoxicity (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.

Patients with Impaired Hepatic Function

TRIZIVIR[®] is contraindicated for use in hepatically impaired patients (see CONTRAINDICATIONS section). 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 some 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 5-6) 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. Dosage reduction of abacavir is therefore required in patients with mild hepatic impairment. The pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment.

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.

Patients co-infected with Hepatitis B virus

Clinical trial and marketed use of lamivudine, have shown that some patients with chronic hepatitis B virus (HBV) disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine, which may have more severe consequences in patients with decompensated liver disease. If TRIZIVIR[®] is discontinued in a patient with HIV and HBV co-infection, 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.

Immune

Patients receiving TRIZIVIR[®] or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close observation by physicians experienced in the treatment of patients with HIV associated diseases.

Immune Reconstitution: During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB) which may necessitate further evaluation and treatment.

Therapy Experienced Patients

In clinical trials, patients with prolonged prior nucleoside reverse transcriptase inhibitor (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy experienced patients (see MICROBIOLOGY: Cross Resistance section).

In heavily pre-treated NRTI patients, the reduction in viral load with abacavir sulfate was very low. The degree of viral load reduction as part of a new combination regimen will depend on the nature and duration of prior therapy which may have selected for HIV-1 variants with cross resistance to abacavir.

Ophthalmologic

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

Patients with impaired renal function may be at a greater risk of toxicity from TRIZIVIR[®] due to decreased renal clearance of lamivudine and zidovudine. Therefore a dosage adjustment of lamivudine and zidovudine may be necessary. The pharmacokinetic properties of abacavir have not been determined in patients with impaired renal function. Other drugs that are eliminated by acyl glucuronide formation are known to accumulate in patients with renal impairment, therefore it is possible the 5'-glucuronide and 5'-carboxylic acid metabolites of abacavir might accumulate in patients with impaired renal function.

It is recommended that TRIZIVIR[®] not be used in patients with reduced renal function (creatinine clearance \leq 50 mL/min). For these patients, it is recommended that abacavir, lamivudine and zidovudine be administered. The individual Product Monographs for abacavir, lamivudine and zidovudine should be consulted for appropriate dosage adjustments.

TRIZIVIR[®] is contraindicated in patients with end-stage renal disease (see CONTRAINDICATIONS section).

Respiratory

Severe respiratory symptoms, some indicative of adult respiratory distress syndrome (ARDS), occur in a small proportion of hypersensitivity reaction cases. ARDS or respiratory failure appear more likely to occur in a re-challenge situation.

Special Populations

Pregnant Women

The safety of TRIZIVIR[®] in human pregnancy has not been established.

Lamivudine, abacavir and zidovudine have been associated with findings in animal reproductive studies. Therefore, administration of TRIZIVIR[®] in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the fetus (see TOXICOLOGY: Reproduction and Teratology section).

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

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

To monitor maternal-fetal outcomes of pregnant women exposed to TRIZIVIR[®], an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling ViiV Healthcare Shire Canada's Drug Safety Department (1-877-393-8448).

Nursing Women

It is recommend that HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV. It is therefore recommended that mothers do not breast feed their babies while receiving treatment with TRIZIVIR[®].

Both lamivudine and zidovudine are excreted in human milk at similar concentrations to those found in serum. It is expected that abacavir will also be secreted into human milk, although this has not been confirmed.

Pediatrics

TRIZIVIR[®] is not recommended in children. There are no data on the use of TRIZIVIR[®] in pediatric patients (see DETAILED PHARMACOLOGY: Pharmacokinetics section).

Geriatrics

Clinical studies of TRIZIVIR[®] did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Hypersensitivity Reactions:

Fatal hypersensitivity reactions have been associated with therapy with abacavir sulfate. Therapy with TRIZIVIR[®] or any medicinal product containing abacavir, **must not** be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Patients developing signs or symptoms of hypersensitivity should discontinue treatment as soon as a hypersensitivity reaction is first suspected, and must seek medical evaluation immediately. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, TRIZIVIR[®] should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications). TRIZIVIR[®], or any other medicinal product containing abacavir should not be restarted even if a recurrence of symptoms occurs following rechallenge with alternative medication(s).

Severe or fatal hypersensitivity reactions can occur within hours after TRIZIVIR[®] re-introduction in patients who have no identified history or unrecognized symptoms of hypersensitivity during their initial period of use of TRIZIVIR[®] (see WARNINGS AND PRECAUTIONS).

Regardless of a patient's HLA-B*5701 status, if therapy with TRIZIVIR[®] or any other medicinal product containing abacavir has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. If a hypersensitivity reaction can not be ruled out TRIZIVIR[®] or any other medicinal product containing abacavir (e.g. ZIAGEN[®], KIVEXA[®]) should not be restarted.

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.

Hypersensitivity Reactions

Overall, in clinical trials conducted before the introduction of screening for the HLA-B*5701 allele, hypersensitivity to abacavir was reported in approximately 8% of patients in 9 clinical trials (range: 2% to 9%). This reaction is characterized by the appearance of symptoms indicating multi-organ / body-system involvement. Symptoms can occur at any time during therapy however they usually appear within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir.

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.

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

| | |
|--------------------------------|---|
| Gastrointestinal tract | Abdominal pain, diarrhea, mouth ulceration, nausea, vomiting |
| Hematological | Lymphopenia |
| Liver/pancreas | Elevated liver function tests, hepatic failure |
| Miscellaneous | Anaphylaxis, conjunctivitis, edema, fatigue, fever, hypotension, lymphadenopathy, malaise |
| Musculoskeletal | Arthralgia, elevated creatine, myalgia, phosphokinase, rarely myolysis |
| Neurological/Psychiatry | Headache, paresthesia |
| Respiratory tract | Adult respiratory distress syndrome, cough, dyspnea, respiratory failure, sore throat |
| Skin | Rash (usually maculopapular or urticarial) |
| Urology | Elevated creatinine, renal failure |

Some patients who experienced a hypersensitivity reaction were initially thought to have acute onset or worsening respiratory disease. The diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of acute onset respiratory diseases, even if alternative respiratory diagnoses (pneumonia, bronchitis, pharyngitis) or flu-like illness, gastroenteritis or reactions to other medications are possible.

Symptoms worsen with continued therapy, and usually resolve upon discontinuation of TRIZIVIR[®] (abacavir sulfate/lamivudine/zidovudine).

Restarting TRIZIVIR[®] or any other medicinal product containing abacavir following a hypersensitivity reaction results in a prompt return of symptoms within hours.

This recurrence of the hypersensitivity reaction maybe more severe than on initial presentation, and may include life-threatening hypotension and death.

Regardless of their HLA-B*5701 status, patients who develop this hypersensitivity reaction must discontinue TRIZIVIR[®] and must never be rechallenged with TRIZIVIR[®] or any other medicinal product containing abacavir (e.g. ZIAGEN[®], KIVEXA[®]).

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 Redistribution/accumulation of body fat | Lactic acidosis, hyperlactatemia Redistribution/accumulation of body fat | Lactic acidosis, hyperlactatemia Redistribution/accumulation of body fat |
| 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 CD₄ cell counts less than 100/mm³. Dosage reduction or cessation of therapy may become necessary (see WARNINGS AND PRECAUTIONS section).

The incidence of neutropenia was also increased in those patients whose neutrophil counts, hemoglobin levels and serum vitamin B₁₂ levels were low at the start of zidovudine therapy.

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving 3TC[®] alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (NUCA2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with 3TC[®]. Three of these patients died of complications of pancreatitis. In a second open-label study (NUCA2005), 12 patients (18%) developed pancreatitis. In study ACTG300, pancreatitis was not observed in 236 patients randomized to 3TC[®] plus RETROVIR[®] (AZT). Pancreatitis was observed in one patient in this study who received open-label 3TC[®] in combination with RETROVIR[®] (AZT) and ritonavir following discontinuation of didanosine monotherapy.

Post-Market Adverse Drug Reactions

The following events have been identified during use of TRIZIVIR[®] in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. 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: | Redistribution/accumulation of body fat (see WARNINGS AND PRECAUTIONS: Endocrine and Metabolism section). |
| Cardiovascular: | cardiomyopathy |
| Digestive: | stomatitis |
| Endocrine and Metabolic: | lactic acidosis, hyperglycemia, hyperlactemia |
| Gastrointestinal: | oral mucosal pigmentation |
| Hemic and Lymphatic: | 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 |
| Musculoskeletal: | myalgia, arthralgia, CPK elevation, rhabdomyolysis |
| 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 |

Serious Adverse Reactions

Abacavir

A patient with a diagnosis of AIDS dementia and a history of seizure disorder experienced a seizure 3 days after stopping abacavir therapy. In the absence of an autopsy, a definitive diagnosis could not be adequately made, and a possible relationship to abacavir therefore could not be ruled out.

Lamivudine

Several serious adverse events have been reported with use of lamivudine in clinical practice. Reports of anaphylaxis, rhabdomyolysis and peripheral neuropathy have been rare (< 1 in 1,000).

Zidovudine

Several serious adverse events have been reported with use of zidovudine in clinical practice. Reports of pancreatitis, sensitization reactions (including anaphylaxis in one patient), vasculitis and seizures have been rare. These adverse events, except for sensitization, have also been associated with HIV disease. Changes in skin and nail pigmentation have been associated with the use of zidovudine.

Coadministration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the toxicity of either drug may be potentiated (see DRUG INTERACTIONS section).

DRUG INTERACTIONS

Overview

Dosage Adjustments

Separate preparations of abacavir, lamivudine and zidovudine should be administered where dosage adjustment is necessary. In these cases the physician should refer to the individual Product Monographs.

No clinically significant changes to pharmacokinetic parameters were observed for abacavir, lamivudine or zidovudine when administered together. 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[®]. The interactions listed below should not be considered exhaustive but are representative of the classes of medicinal products where caution should be exercised.

Drug-Drug Interactions

Interactions Relevant to Abacavir

Based on the results of *in vitro* experiments and the known major metabolic pathways of abacavir sulfate, the potential for drug interactions involving abacavir sulfate is low. Abacavir sulfate shows low potential to inhibit metabolism mediated by the cytochrome P₄₅₀ 3A4 enzyme. It has also been shown *in vitro* not to interact with drugs that are metabolised by CYP3A4, CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for drug interactions with antiretroviral protease inhibitors and other drugs metabolised by major P₄₅₀ enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir sulfate, zidovudine and lamivudine.

Table 2 Established or Potential Drug-Drug Interactions Relevant to Abacavir

| Proper name | Effect | Clinical comment |
|--------------------|--|---|
| Ethanol | In men, the metabolism of abacavir sulfate is altered. | 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 | Changes in abacavir pharmacokinetics. | In a pharmacokinetic study, coadministration of 600 mg abacavir twice daily and methadone showed a 35% reduction in abacavir C _{max} and a 1 hour delay in t _{max} , but AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study abacavir increased 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 | Interaction with elimination is possible. | Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied. |

Interactions Relevant to Lamivudine

Zidovudine plasma levels are not significantly altered when coadministered with lamivudine. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Table 3 **Established or Potential Drug-Drug Interactions Relevant to Lamivudine**

| Proper name | Effect | Clinical comment |
|--------------------|--|---|
| Trimethoprim | Administration of trimethoprim, a constituent of co-trimoxazole, causes a 40% increase in lamivudine plasma levels. | However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of co-trimoxazole. Administration of co-trimoxazole with the lamivudine/ zidovudine combination in patients with renal impairment should be carefully assessed. |
| Zalcitabine | Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. | Lamivudine is not recommended to be used in combination with zalcitabine. |

The possibility of interactions with other drugs administered concurrently should be considered, particularly when the main route of elimination is renal.

Interactions Relevant to Zidovudine

Other 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.

Table 4 Established or Potential Drug-Drug Interactions Relevant to Zidovudine

| 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. |

Table 4 Established or Potential Drug-Drug Interactions Relevant to Zidovudine

| Proper name | Effect | Clinical comment |
|-------------|--|--|
| 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 $39\% \pm 62\%$ (mean \pm 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. |

Table 4 Established or Potential Drug-Drug Interactions Relevant to Zidovudine

| Proper name | Effect | Clinical comment |
|--------------------|---|--|
| 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. |
| Ribavirin | 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 significance 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. |

Table 4 Established or Potential Drug-Drug Interactions Relevant to Zidovudine

| Proper name | Effect | Clinical comment |
|--------------|--------|--|
| Other agents | | <p>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.</p> <p>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.</p> |

Table 4 Established or Potential Drug-Drug Interactions Relevant to Zidovudine

| Proper name | Effect | Clinical comment |
|---------------|--------|--|
| Miscellaneous | | <p>Other medicinal products, including but not limited to, acetylsalicylic 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[®].</p> <p>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.</p> |

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended oral dose of TRIZIVIR[®] (abacavir sulfate/lamivudine/zidovudine) is one tablet twice daily.

TRIZIVIR[®] can be taken with or without food.

Dose Adjustment

It is recommended that separate doses of abacavir, lamivudine and zidovudine be administered to patients with reduced renal function (see WARNINGS AND PRECAUTIONS section), patients who weigh less than 50 kg or patients requiring dosing adjustments due to adverse events. See complete prescribing information for abacavir, lamivudine and zidovudine for dosage adjustments.

Missed Dose

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

OVERDOSAGE

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

There is no known antidote for TRIZIVIR[®] (abacavir sulfate/lamivudine zidovudine).

If overdosage occurs, the patient should be monitored, and standard supportive treatment applied as required. Although no data is available, administration of activated charcoal may be used to aid in the removal of unabsorbed drug. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. 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.

One case of acute overdose in an adult ingesting 6 g of 3TC[®] was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. One other adult patient in error ingested lamivudine 1,200 mg per day plus zidovudine 1,200 mg per day for approximately 2 weeks; he had a Grade 3 decrease in absolute neutrophil count that resolved upon reduction of doses of lamivudine and zidovudine. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of 3TC[®]; the second case involved the use of 5 mg/kg of 3TC[®] twice daily for 30 days. There were no clinical signs or symptoms noted in either case.

In Phase I studies, lamivudine was administered at doses up to 20 mg/kg per day (i.e. approximately five times the usual recommended dose in adults) without serious consequences.

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

Abacavir sulfate, lamivudine and zidovudine are inhibitors of HIV-1 and HIV-2 replication *in vitro*. Abacavir is a synthetic carbocyclic nucleoside analogue. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Zidovudine is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido (-N₃) group. Intracellularly, abacavir, lamivudine and zidovudine are phosphorylated to their active 5'-triphosphate metabolites, carbovir-triphosphate, lamivudine triphosphate and zidovudine triphosphate. The principal mode of action of carbovir, lamivudine and zidovudine triphosphate is inhibition of HIV reverse transcription (RT) via viral DNA chain termination. Carbovir, lamivudine and zidovudine triphosphate show significantly less affinity for host cell DNA polymerases.

Pharmacokinetics

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. 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 \pm 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.

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 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

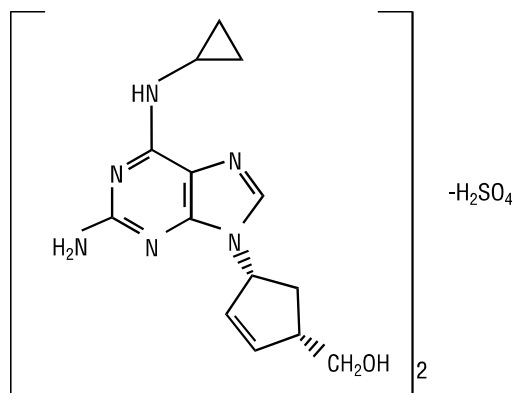
Drug Substance

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: pK₁ = 0.4, pK₂ = 5.06.

Melting point: 219°C followed by decomposition.

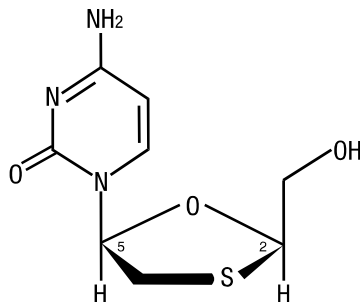
Drug Substance

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.

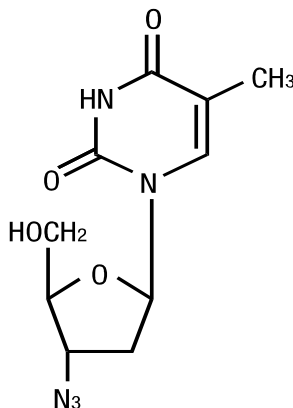
Drug Substance

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

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 5.

Table 5 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 section). 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 $86\% \pm 25\%$ (mean \pm SD). After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{\max}) was $3.0 \pm 0.89 \mu\text{g/mL}$ (mean \pm SD) and AUC_(0-12 hours) was $6.02 \pm 1.73 \mu\text{g}\cdot\text{h/mL}$.

Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was $86\% \pm 16\%$ (mean \pm SD) for the tablet and $87\% \pm 13\%$ 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 $64\% \pm 10\%$ (mean \pm 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 $1.3 \pm 0.4 \text{ L/kg}$, 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 ($\sim 49\%$) 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 $\mu\text{g/mL}$, 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 IC₅₀ 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 \pm 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 \pm SD), representing $71\% \pm 16\%$ (mean \pm 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 ($t_{1/2}$) ranged from 5 to 7 hours. Oral clearance was 0.37 ± 0.05 L/hr/kg (mean \pm 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

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 section).

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 6.

Table 6 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)

| | 6 | 4 | 6 |
|--------------------------------|-------------|--------------|-------------|
| Number of subjects | > 60 mL/min | 10-30 mL/min | < 10 mL/min |
| Creatinine clearance criterion | | | |
| 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 section).

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 section).

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).

Clinical Trials:

CNAAB3005 is 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 CD₄ cell count was 360 cells/mm³, and median plasma HIV-1 RNA was 4.83 log₁₀ 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.

MICROBIOLOGY

Virology

Abacavir, lamivudine and zidovudine are potent, selective inhibitors of HIV-1 and HIV-2 replication *in vitro*. Lamivudine is the (-) enantiomer of a dideoxy analogue of cytidine. Zidovudine is a thymidine analogue in which the 3'-hydroxy (-OH) group is replaced by an azido (-N₃) group. Intracellularly, abacavir, lamivudine and zidovudine are phosphorylated to their active 5'-triphosphate metabolites, carbovir-triphosphate (CBV-TP) lamivudine triphosphate (L-TP) and zidovudine triphosphate (ZDV-TP). *In vitro* L-TP and ZDV-TP have an intracellular half-life of approximately 10.5 to 15.5 hours and 3 hours respectively. The principal mode of action of L-TP and ZDV-TP is inhibition of HIV reverse transcription (RT) via viral DNA chain termination. L-TP is a weak inhibitor of mammalian α , β and γ -DNA polymerases. ZDV-TP is a weak inhibitor of the cellular DNA polymerase- α and mitochondrial polymerase- γ and has been reported to be incorporated into the DNA of cells in culture.

In Vitro Activity

The relationships between *in vitro* susceptibility of HIV to abacavir, lamivudine and zidovudine and the inhibition of HIV replication in humans or clinical response are still being investigated. The anti-HIV activity of nucleoside analogues *in vitro* can vary depending on the viral strain, cell type and assay used to measure such activity. To assess the activity of abacavir, lamivudine and zidovudine, a number of virus/cell combinations were used, and inhibitory activity was measured in different assays by determination of IC₅₀ and IC₉₀ values. Abacavir, lamivudine and zidovudine demonstrated anti-HIV-1 activities in all virus/cell combinations tested. However, zidovudine activity was substantially less in chronically infected cell lines.

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 (IC₅₀) ranged from 3.7 to 5.8 μ M against HIV-1 IIIB, and was $0.26 \pm 0.18 \mu$ M (1μ M = 0.28μ g/mL) against eight clinical isolates. The IC₅₀ of abacavir against HIV-1 BaL varied from 0.07 to 1.0 μ M. Abacavir had synergistic activity in combination with amprenavir, nevirapine or zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine or zalcitabine *in vitro*. These drug combinations have not been adequately studied in humans. The relationship between *in vitro* susceptibility of HIV to abacavir and the inhibition of HIV replication in humans has not been established.

Lamivudine

The antiviral activity of lamivudine has been studied in combination with other antiretroviral compounds (zidovudine, zalcitabine, and didanosine) using HIV-1-infected MT-4 cells as the test system. The MTT formazan assay demonstrated synergistic antiretroviral activity between lamivudine and zidovudine, additive antiretroviral activity between lamivudine and zalcitabine and additive antiretroviral activity between lamivudine and didanosine. The combination of lamivudine/zidovudine also showed synergistic activity in a variable-ratio study.

Zidovudine

Zidovudine blocked 90% of detectable HIV replication *in vitro* at concentrations of $\leq 0.13 \mu\text{g/mL}$ (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 $0.013 \mu\text{g/mL}$ (ID_{50}) in both HIV-infected H9 cells and peripheral blood lymphocytes. Zidovudine at concentrations of $0.13 \mu\text{g/mL}$ 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 ($8.8 \mu\text{g/mL}$ in one laboratory to $13.3 \mu\text{g/mL}$ 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 $0.013 \mu\text{g/mL}$ and ID_{95} sensitivity values between 0.03 to $0.3 \mu\text{g/mL}$.

Drug Resistance

Abacavir

Abacavir-resistant isolates of HIV-1 have been selected *in vitro* and are associated with specific genotypic changes in the RT coding region (codons K65R, L74V, Y115F and M184V). *In vitro* selection for resistance to abacavir occurs relatively slowly and requires multiple mutations. 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 abacavir and zidovudine delays the emergence of mutations associated with resistance to abacavir compared with monotherapy with abacavir. Phenotypic analysis of HIV-1 isolates that harbour abacavir-associated mutations from 17 patients after 12 weeks of abacavir monotherapy exhibited a 3-fold decrease in susceptibility to abacavir *in vitro*. The clinical relevance of genotypic and phenotypic changes associated with abacavir therapy has not been established.

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. 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 [³H]-thymidine uptake (Td) assays. In the CP assay, lamivudine was the least toxic of the four compounds. [³H]-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 [³H]-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. ID₅₀ 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 ID₅₀ of 5 µg/mL. Moreover, in a colony-forming unit assay designed to assess the toxicity of zidovudine for human bone marrow, an ID₅₀ 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 BID (12 mg (base)/kg/day for a 50 kg person). The results are summarized in Table 7.

Table 7 Median Lethal Doses of Abacavir in Mice and Rats Following Oral and Intravenous Administration

| Species (strain) | Route of Administration | Sex | Median Lethal Dose (mg/kg) | | Multiple of Therapeutic Dose* |
|------------------|-------------------------|--------|----------------------------|---------|-------------------------------|
| | | | Succinate | Base | |
| Mouse (CD-1) | Oral | Male | 1,731.68 | 1,226 | 102 |
| | | Female | > 1,900 | 1,345 | 112 |
| | Intravenous | Male | > 260 | > 184 | > 15 |
| | | Female | > 260 | > 184 | > 15 |
| Rat (CD) | Oral | Male | > 2,000 | > 1,416 | 118 |
| | | Female | > 2,000 | > 1,416 | 118 |
| | Intravenous | Male | > 260 | > 184 | > 15 |
| | | Female | > 260 | > 184 | > 15 |

Key: * =Median lethal dose/ therapeutic dose (300 mg (base) b.i.d., equivalent to 12 mg (base)/kg/day based on 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. Microscopically, slight centrilobular hepatocellular hypertrophy was seen in these animal species. Occasional individual cell necrosis, pigment deposits in centrilobular hepatocyte and Kupffer cells were seen in mice and rats. In high dose monkeys, slightly swollen mitochondria, a decrease in the amount of rough endoplasmic reticulum and an increase in the number of lysosomes was observed using electron microscopy.

The results are summarized in Table 8.

Table 8 Findings in Mice, Rats and Monkeys Following Long-Term Oral Administration of Abacavir

| Species (Strain) Report No. [Salt used] | Study Duration | Number of Animals/Group | | Dosage (mg/kg/day) | | Toxic Effects Observed |
|--|----------------|-------------------------|----------------|--------------------|-----------------|---|
| | | Males | Females | Salt | Base | |
| Mouse (CD1) RD1996/00245/00 [Abacavir succinate] | 6 months | 30 30 40 | 30 30 40 | 55 110 330 | 39 78 234 | Very slight increase in serum cholesterol in males at 110 mg and both sexes at 330 mg. Increased liver weight and hepatocellular hypertrophy seen at 330 mg. Dose-related and reversible increases in endogenous pigment deposition in Kupffer cells and centrilobular hepatocytes. Very slight increase in cecal crypt epithelial cell apoptosis associated with submucosal inflammation at 330 mg. |
| Rat (Han Wistar) RD1997/03595/00 [Abacavir hemisulfate] | 3 months | 5 5 5 | 5 5 5 | 35 135 530 | 25 96 375 | Slight decreases in serum albumin and total protein and a slight increase in serum cholesterol at 530 mg. Very slight decrease in serum albumin in females at 135 mg. Slight increase in liver weight, centrilobular hepatocellular hypertrophy and accumulation of brown pigment in Kupffer cells at 530 mg. Similar liver changes also observed in males at 135 mg. Trace hypertrophy of thyroid follicular epithelium and germ cell loss in testes at 530 mg. |
| Monkey (Cynomolgus) RD1996/00310/01 [Abacavir succinate] | 12 months | 7 7 9 | 7 7 9 | 50 140 300† | 35 99 212 | Emesis at 420 mg decreased when dosage reduced to 300 mg. Hunched posture, hypoactivity, decreased appetite and/or abnormal or reduced fecal output seen at 420 mg, but not at 300 mg. Reduced body weight gain at 420/300 mg during first 5-6 weeks of treatment. Transient reductions in erythrocyte count (females only), hemoglobin concentration and hematocrit and an increase in reticulocyte count at 420 mg, but these changes not seen at 300 mg. Increased liver weight and hepatocellular hypertrophy seen at 300 mg, with some evidence of an effect at lower dosages. Ultrastructural liver changes included slightly swollen mitochondria, decreased rough endoplasmic reticulum and an increase in lysosomes at 300 mg. Slight increases in serum alanine aminotransferase and triglycerides probably related to the liver changes. |

Key: † = Initially 420 mg/kg/day, but reduced to 300 mg/kg/day on day 36 due to unacceptable toxicity.

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

The results of long term toxicity studies with zidovudine in rats, dogs and monkeys are presented in the table below. Rats and monkeys received zidovudine by gavage, dogs were administered zidovudine capsules.

Table 9 Long Term Toxicity Studies with Zidovudine in Rats, Dogs and Monkeys

| Species | No. per Group | | Dose Levels (mg/kg/day) | Duration (weeks) | Effects |
|---------------------|---------------|----|-------------------------|------------------|--|
| | M | F | | | |
| CD Rat | 5 | 5 | 0, 60, 125, 250, 500 | 2 | Post-dose salivation. Weight loss in mid dose (1/5) and high dose (1/5) males. |
| CD Rat | 12 | 12 | 0, 56, 167, 500 | 13 | Anogenital staining in high dose rats. Increased blood glucose levels in high dose females at term. Occasional decreases in SGOT in both sexes at high dose. |
| CD Rat | 25 | 25 | 0, 50, 150, 450 | 52 | Salivation at high dose for the first 4 weeks. Moderate, reversible macrocytic anemia, with reticulocytosis, in the high dose animals. Increased urine output in some high dose animals. |
| Dog | 1 | 1 | 0, 125, 250, 500 | 2 | High dose female sacrificed day 14, following 2 days emesis. High dose male had bloody vomitus on days 11, 14, 16. Marked leukopenia and thrombocytopenia in all treated dogs, most severe in high dose. Alk. phos., BUN and creatinine increased in high dose female. Slight increase in kidney weight in both high dose dogs and in mid dose male. Focal to diffuse hemorrhage in GI tract and mesentery of both high dose dogs and mid dose female. Moderate hypoactivity in the lymph nodes, involution of the thymus (mid and high dose females, high dose male) and splenic lymphoid atrophy (high dose male only). Dose related mild to marked hypocellularity of the bone marrow at all dose levels. |
| Monkey (Cynomolgus) | 1 | 1 | 0, 125, 250, 500 | 2 | Emesis in high dose male. Decreased RBC, hematocrit and hemoglobin in all groups (all values within normal range). Increased SGPT in mid and high dose males, more marked in high dose females. |
| Monkey (Cynomolgus) | 4 | 4 | 0, 34, 100, 300 | 13 | Emesis in one high dose male. Mild to moderate decrease in RBC, HCT and HB; slight to mild increase in MCV in mid and high dose groups. Slight decrease in WBC in high dose males. |
| Monkey (Cynomolgus) | 5 | 5 | 0, 35, 100, 300 | 26 | Decreased RBC, HCT and HB in all groups, generally dose-related. Increase in MCV and MCH more prominent in males. Dose related retardation of bone marrow cell maturation, particularly in erythroid elements. Slight, inconsistent increase in platelets in mid and high dose group. |
| Monkey (Cynomolgus) | 6 | 6 | 35, 100, 300 | 52 | Dose related macrocytic anemia (i.e. decreased RBC, HCT and HB, increased MCV and MCH) maximized by week 26 at latest. After 4 weeks recovery, the bone marrow smears were similar in control and treated animals. The severity of anemia was similar to that in the 3 month and 6 month study. |

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 vitro* 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.

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 F₀ and F₁ generation animals, and the development of the F₁ and F₂ 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.

Peri- and Post-Natal Studies

A separate peri- and post-natal study was conducted in pregnant rats given doses of 0, 50, 150 and 400 mg/kg/day 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 F₁ 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 sulfate/lamivudine/zidovudine**

This leaflet is part III of a three-part "Product Monograph" published when TRIZIVIR[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet contains important information about your treatment with TRIZIVIR[®]. Please read this leaflet carefully before you start to take your medicine. 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 name of your medicine is TRIZIVIR[®] (abacavir sulfate/lamivudine/zidovudine). TRIZIVIR[®] is a treatment that contains a combination of three active ingredients that are currently available as separate medicines: ZIAGEN[®] (abacavir sulfate), 3TC[®] (lamivudine) and RETROVIR[®] (AZT) (zidovudine). TRIZIVIR[®] can only be obtained with a prescription from your doctor. You should not be taking ZIAGEN[®], RETROVIR[®] (AZT), KIVEXA[®] or 3TC[®] while taking TRIZIVIR[®].

What it does:

The Human Immunodeficiency Virus (HIV) is a retrovirus. Infection with HIV damages the immune system and can lead to Acquired Immune Deficiency Syndrome (AIDS) and other related illnesses.

TRIZIVIR[®] is an antiretroviral medication. TRIZIVIR[®] does not cure AIDS or kill the HIV virus, but helps to prevent further damage to the immune system by slowing down production of new viruses.

When it should not be used:

Do not take TRIZIVIR[®].

- If you have previously had an allergic reaction to TRIZIVIR[®] or to the active ingredients abacavir (ZIAGEN[®] or KIVEXA[®]), lamivudine (3TC[®] or KIVEXA[®]) or zidovudine (RETROVIR[®] (AZT)) or any of the ingredients found in TRIZIVIR[®]
- If you have end-stage kidney disease
- If you have liver disease.
- If you have a very low red blood cell count (anemia) or very low white blood cell count (neutropenia).

What the medicinal ingredient is:

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[®] is available in a tablet containing 300 mg abacavir, 150 mg of lamivudine and 300 mg zidovudine.

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions****Hypersensitivity Reaction**

Patients taking TRIZIVIR[®] may develop a hypersensitivity reaction (serious allergic reaction) which **can be life threatening** if you continue to take TRIZIVIR[®].

Your risk of this allergic reaction is much higher if you have a gene variation called HLA-B*5701 than if you do not. Your doctor can determine with a blood test if you have this gene variation. Even if you don't have this gene variation, you may still experience this type of allergic reaction.

If you have two or more of the following sets of symptoms, you may be having this kind of reaction:

- Fever
- Rash
- Nausea, vomiting, diarrhea, or abdominal pain
- General ill feeling, extreme tiredness or achiness
- Shortness of breath, cough or sore throat

A written list of these symptoms is on the Warning Card provided by your pharmacist. You should carry this Warning Card with you. **If you notice these symptoms while taking TRIZIVIR[®], stop taking TRIZIVIR[®] and call your doctor immediately.**

If you have had this reaction to **TRIZIVIR[®]**, **never take any medicine containing abacavir, such as TRIZIVIR[®] or ZIAGEN[®] or KIVEXA[®] again regardless of whether you have the HLA-B*5701 gene variation**, as **within hours** you may experience a **life threatening lowering of your blood pressure or death.**

It is important if you have stopped taking TRIZIVIR[®] either on medical advice or because you think you are having side effects or due to other illness, that you **contact your doctor for advice** before restarting TRIZIVIR[®]. Your doctor will check whether any symptoms you had before stopping may be related to this hypersensitivity reaction. If your doctor has any doubt about this, you will be advised **never to take any medicine containing abacavir, such as TRIZIVIR[®], KIVEXA[®] or ZIAGEN[®] again.**

WARNINGS AND PRECAUTIONS

Pancreatitis (inflammation of the pancreas) has been observed in patients receiving abacavir and lamivudine (See Other Special Warnings).

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

About 8 in every 100 patients, who are treated with TRIZIVIR[®], develop a hypersensitivity reaction to the active ingredient abacavir. The symptoms **of a hypersensitivity reaction to the active ingredient of TRIZIVIR[®], abacavir**, usually include fever and a skin rash.

Other frequently observed signs and symptoms include nausea, vomiting, diarrhea, abdominal pain, shortness of breath, cough, headache, and severe tiredness. Other symptoms may include sore throat, joint or muscle pain and swelling of the neck.

Occasionally inflammation of the eye (conjunctivitis), ulcers in the mouth or low blood pressure may occur. The symptoms of this allergic reaction usually occur in the first six weeks of treatment with TRIZIVIR[®], but may occur at any time, and get worse with continued treatment.

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/ reoccur. Your doctor will monitor your conditions for several months after stopping treatment with TRIZIVIR[®].

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

- About all your medical conditions.
- If you have kidney or liver disease or hepatitis B.
- If you have been tested and know whether or not you have a gene variation HLA-B*5701.
- You are taking ribavirin as it could cause or worsen anemia (symptoms of tiredness, shortness of breath).
- If you are pregnant or breastfeeding.
- About all the medicines you are taking including vitamins, herbal supplements and nonprescription drugs.

Other Special Warnings

Nucleoside Reverse Transcriptase Inhibitors (NRTIs), the class of medicines to which TRIZIVIR[®] belongs, 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. In some cases, this condition can be fatal. Women are more likely than men to experience this rare but serious side effect. 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.

Inflammation in the pancreas (pancreatitis) has been reported in some patients treated with abacavir, lamivudine and zidovudine, although it was not clear whether this was due to the medicine or the HIV infection itself. If your doctor detects clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis, they will stop treatment with TRIZIVIR[®] immediately.

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 is due to suddenly stopping the active substance 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.

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.

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[®].

It is important that your doctor knows about all your symptoms even if you think they are not related to HIV infection. Your doctor may need to change the dose of your medicine.

Use Of This Medicine During Pregnancy And Breast Feeding:

If you are pregnant, or likely to become pregnant soon, or if you are breast feeding, please inform your doctor before taking any drugs, including TRIZIVIR[®].

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

There have been very rare reports of diseases that affect the nervous system such as delayed development and seizures.

These findings do not affect current recommendations to use antiretroviral therapy in pregnant women to prevent transmission of HIV to their babies.

You are recommended not to breast feed your baby while taking TRIZIVIR[®]. Additionally it is recommended that HIV infected women do not breast feed their infants under any circumstances in order to avoid transmission of HIV from mother to child.

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 zalcitabine.

It is important to tell your doctor if you are taking any of the medicines below (ask your doctor if you are not sure)

- Phenytoin, valproic acid, Phenobarbital, 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 and doxorubicin
- Clarithromycin

If you are taking methadone, your doctor may need to adjust your methadone dose, as abacavir (one of the active substances in TRIZIVIR®) 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 your medicine as your doctor had advised you. The label on it will usually tell you the amount to take, and how frequently. If it does not, or you are not sure, ask your doctor or pharmacist.

Adults

As a general rule, swallow one tablet twice a day. TRIZIVIR® can be taken with or without food.

If your doctor wishes to reduce your dose of TRIZIVIR®, for example if you have kidney problems, then your medicine may be changed to abacavir, lamivudine and zidovudine taken as separate medicines, ZIAGEN®, 3TC® and RETROVIR® (AZT).

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:

Accidentally taking too much of your medicine is unlikely to cause any serious problems. However, you should **immediately** contact your doctor, your hospital emergency department or the nearest poison control centre.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All medicines may cause some side effects. When treating HIV infection it is not always possible to tell whether any side effects that occur are caused by TRIZIVIR®, by other medicines you are taking at the same time, or by the HIV disease.

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.
- 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.

Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breasts, and around the trunk. Loss of fat from the legs, arms, and face may also happen.

The cause and long term health effects of these conditions are not known at this time.

Always tell your doctor or pharmacist about any new symptoms, even those not mentioned in this leaflet. If you feel ill in any other way that you do not understand, tell your doctor or pharmacist.

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

| Frequency | Side Effect/ Symptoms (2 or more of the following) | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|-----------------|--|-------------------------------------|--------------|---|
| | | Only if severe | In all cases | |
| Common | Allergic reactions and symptoms such as fever, rash, nausea, vomiting, diarrhea, or abdominal pain, generally ill feeling, extreme tiredness or achiness, shortness of breath, cough or sore throat. | | | X |
| Uncommon | Blood problems and symptoms such as anemia (lowered red blood cell count – resulting in fatigue, breathlessness, low white blood cell count making you more prone to infections). | | | X |
| Rare | Pancreatitis (inflammation of the pancreas) and symptoms such as nausea, vomiting, and severe stomach cramps. | | | X |

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

| Frequency | Side Effect/ Symptoms (2 or more of the following) | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|-------------|--|-------------------------------------|--------------|---|
| | | Only if severe | In all cases | |
| Rare | Lactic acidosis (high level of acid in the blood) and symptoms such as 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 |

This is not a complete list of side effects. For any unexpected effects while taking TRIZIVIR[®], contact your doctor or pharmacist.

HOW TO STORE IT

Store TRIZIVIR[®] tablets between 15° and 30°C.

As with all medicines, keep TRIZIVIR[®] out of reach 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 0701C
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

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.

You may need to read this leaflet again. Please do not throw it away until you have finished treatment with TRIZIVIR®.

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 Shire Canada at:

7333 Mississauga Road

Mississauga, Ontario

L5N 6L4

1-877-393-8448

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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 have two or more of the following sets of symptoms while taking TRIZIVIR®, stop taking it and call your doctor immediately:**

| | 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 had this reaction to TRIZIVIR®, **never take any medicine containing abacavir, such as TRIZIVIR® or ZIAGEN® or KIVEXA®** (abacavir sulfate/lamivudine) again. If you take **any medicine containing abacavir, such as TRIZIVIR®, KIVEXA® or ZIAGEN®** 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.