

Abacavir/Lamivudine/ Zidovudine



Brand Name: Trizivir

Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Abacavir/lamivudine/zidovudine (Trizivir) is a fixed-dose tablet that contains three synthetic nucleoside analogues: abacavir sulfate, lamivudine, and zidovudine. Each tablet contains abacavir sulfate 300 mg, lamivudine 150 mg, and zidovudine 300 mg, each of which inhibits HIV-1 viral reverse transcriptase. [1]

HIV/AIDS-Related Uses

Trizivir was approved by the FDA on November 14, 2000, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults or adolescents who weigh more than 40 kg (88 lbs).[2] When used as part of a three-drug HIV treatment regimen, Trizivir should be used with antiretroviral agents from different pharmacological classes and not with other NRTIs.[3]

Pharmacology

Each of the three synthetic nucleoside analogues contained in Trizivir inhibits viral reverse transcriptase (RT), an enzyme HIV requires in order to replicate. Abacavir, lamivudine, and zidovudine work by incorporating themselves into viral DNA and terminating the viral DNA chain. For more information, see individual drug fact sheets for abacavir sulfate, lamivudine, and zidovudine.

Abacavir is a carbocyclic nucleoside analogue that is converted by cellular enzymes to the active metabolite, carbovir triphosphate. Carbovir triphosphate is an analogue of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate inhibits RT by competing with the natural substrate dGTP and by incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation. In vitro, abacavir had synergistic activity in combination with amprenavir, nevirapine, and zidovudine and additive activity with didanosine, lamivudine, stavudine, and zalcitabine. Following oral dosing,

abacavir is rapidly absorbed and extensively distributed. Binding of abacavir to human plasma proteins is about 50%, independent of concentration. Abacavir is primarily eliminated by metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the 5'-glucuronide.[4]

Lamivudine is a synthetic nucleoside analogue that is phosphorylated intracellularly to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). L-TP inhibits viral RT by DNA chain termination. In vitro, lamivudine had synergistic antiretroviral activity with zidovudine. Following oral dosing, lamivudine is rapidly absorbed and extensively distributed. Plasma protein binding is low and about 70% of an intravenous dose is excreted unchanged in the urine. Metabolism is a minor route of elimination.[5]

Zidovudine is phosphorylated intracellularly to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). ZDV-TP also inhibits RT by DNA chain termination. In vitro, zidovudine demonstrates synergistic activity with delavirdine, didanosine, indinavir, nelfinavir, nevirapine, ritonavir, saquinavir, and zalcitabine and additive activity with interferon alfa. Following oral dosing, zidovudine is rapidly absorbed and extensively distributed. Plasma protein binding is low and elimination is primarily by hepatic metabolism. The major metabolite is 3'-azido-3'-deoxy-5'-O-beta-D-glucopyranuronosylthymidine. A second metabolite, 3'-amino-3'-deoxythymidine, has been identified.[6]

In a bioavailability study of Trizivir compared to separate tablets of the three components given simultaneously to healthy adults, there was no difference in absorption. One Trizivir tablet was bioequivalent to dosing with one tablet each of abacavir sulfate 300 mg, lamivudine 150 mg, and zidovudine 300 mg in healthy, fasting adults.[7]

Trizivir is in FDA Pregnancy Category C. No adequate or well-controlled studies of the combination drug have been done in pregnant women. A study of zidovudine therapy in women in the last trimester of pregnancy showed that

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Pharmacology (cont.)

although this drug does cross the placenta, there was no evidence of drug accumulation, and zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Studies in laboratory animals have shown that abacavir and lamivudine cross the placenta, with evidence of fetal toxicity at dosage levels many times higher than the corresponding dose for humans. Trizivir should be used in pregnancy only if the potential benefits outweigh the risks. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to Trizivir and other antiretrovirals. Physicians may register patients online at <http://www.APRegistry.com> or by calling 1-800-258-4263. Zidovudine is excreted in human milk, and abacavir and lamivudine are excreted in the milk of laboratory animals.[8]

HIV-1 isolates with reduced sensitivity to abacavir, lamivudine, or zidovudine have been selected in vitro and have also been obtained from patients treated with that combination or lamivudine plus zidovudine. Treatment for 12 weeks with lamivudine and zidovudine restored sensitivity to zidovudine in some patients with zidovudine-resistant virus. Combination therapy delayed the emergence of mutations conferring resistance to zidovudine. Higher levels of resistance were associated with greater numbers of mutations. Laboratory strains of HIV-1 containing multiple RT mutations that confer abacavir resistance exhibited cross resistance to lamivudine, didanosine, and zalcitabine in vitro. Cross resistance to didanosine and zalcitabine has been observed in some patients who harbor lamivudine-resistant HIV-1 isolates. Multiple drug resistance, including resistance to lamivudine and stavudine, has been observed in HIV isolates from patients treated for more than 1 year with zidovudine plus didanosine or zalcitabine.[9]

Cross resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine has been seen in patients treated with abacavir. Cross resistance to abacavir, didanosine, tenofovir, and zalcitabine has been seen in patients treated with lamivudine. Multiple drug resistance, including resistance to lamivudine, didanosine, stavudine,

zalcitabine, and zidovudine, has been observed in HIV isolates from some patients treated for more than 1 year with zidovudine plus didanosine or zalcitabine.[10]

Adverse Events/Toxicity

Trizivir contains abacavir sulfate, which has been associated with fatal hypersensitivity reactions. In clinical studies, approximately 5% of adult and pediatric patients who received abacavir developed a hypersensitivity reaction. Hypersensitivity reactions are characterized by symptoms indicating multi-organ/body system involvement, usually appearing within the first 6 weeks of abacavir therapy, although they may appear at any time. Frequently observed signs and symptoms of hypersensitivity include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Other signs and symptoms include malaise, lethargy, myalgia, myolysis, arthralgia, edema, cough, dyspnea, headache, and paresthesia. The diagnosis of hypersensitivity reaction should be considered for patients presenting who present with symptoms of acute onset respiratory diseases such as pneumonia, bronchitis, or flu-like illnesses. Physical findings associated with hypersensitivity reactions include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and sometimes a maculopapular or urticarial rash. Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase or creatinine, and lymphopenia. Anaphylaxis, liver failure, renal failure, hypotension, and death have occurred in association with hypersensitivity reactions. Severe or fatal hypersensitivity reactions can occur within hours after reintroduction of abacavir in patients who have no identified history or who have unrecognized symptoms of hypersensitivity to abacavir. Trizivir should be discontinued permanently if hypersensitivity cannot be ruled out.[11] An Abacavir Hypersensitivity Registry has been established to facilitate reporting of hypersensitivity reactions. Physicians should register patients by calling 1-800-270-0425.[12]

Recently, the genetic HLA B*5701 allele variant has been associated with an increased likelihood of abacavir hypersensitivity reaction. New research

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Adverse Events/Toxicity (cont.)

indicates that a positive result in a genetic test for this variant accurately predicts the hypersensitivity reaction of patients to abacavir, which therefore allows these patients to avoid abacavir use (and hypersensitivity reaction risk) altogether. In the PREDICT-1 study, in which 5.6% of participants were positive for the HLA B*5701 allele, the screening test had a 100% negative predictive value. Screening for HLA B*5701 and removing positive-testing participants from the abacavir treatment arm completely eliminated hypersensitivity reactions in that arm (0% vs. 2.7% in the non-tested control group; $p < 0.001$). An additional study suggests that, although the variant is more common in white than black patients, genetic screening is equally useful in both populations; all five black patients who had confirmed hypersensitivity reactions were positive for the HLA B*5701 allele, which supports the use of testing in this population for the prevention of hypersensitivity reaction.[13] [14] The current recommendations from the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents is to administer genetic testing for the HLA B*5701 variant before beginning treatment with abacavir in HIV infected patients.[15]

Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues alone or in combination. These conditions are sometimes fatal. Female gender, obesity, and prolonged nucleoside exposure may be risk factors. Caution should be exercised in any patient with known risk factors for liver disease; however, liver problems have been reported in patients with no known risk factors. Treatment with Trizivir should be suspended in any patient who develops clinical or laboratory findings that suggest the presence of lactic acidosis or pronounced hepatotoxicity.[16] Neutropenia and anemia are the most frequent adverse effects associated with zidovudine therapy.[17] Myopathy and myositis have occurred with prolonged use of zidovudine and may occur during therapy with Trizivir.[18] Peripheral neuropathy has been reported in adults who receive lamivudine but has rarely resulted in interruption or discontinuance of treatment.[19] Post-treatment exacerbations of hepatitis B virus (HBV) infections have been

reported in both HIV infected and uninfected participants treated with lamivudine for chronic HBV when lamivudine therapy was discontinued.[20]

Immune reconstitution syndrome has been reported with the use of combination anti-HIV therapy, including abacavir/lamivudine/zidovudine. Patients who develop immune system responses to anti-HIV therapy may develop an inflammatory response to residual opportunistic infections (e.g., *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, tuberculosis).[21]

Other adverse effects occurring in clinical trials of Trizivir or its component drugs include nausea, vomiting, diarrhea, abdominal pain or cramping, dyspepsia, anorexia, insomnia and other sleep disorders, fever and/or chills, headache, dizziness, malaise and/or fatigue, depressive disorders, neuropathy, musculoskeletal pain, myalgia, arthralgia, and skin rashes. Adverse events reported during post-approval use of abacavir, lamivudine, and/or zidovudine that may potentially be related to these drugs include cardiomyopathy, stomatitis, oral mucosal pigmentation, gynecomastia, hyperglycemia, vasculitis, weakness, anemia, aplastic anemia, lymphadenopathy, pure red cell aplasia, splenomegaly, lactic acidosis and hepatic steatosis, pancreatitis, post-treatment exacerbation of hepatitis B, sensitization reactions and urticaria, muscle weakness, creatine phosphokinase (CPK) elevation, rhabdomyolysis, paresthesia, peripheral neuropathy, seizures, abnormal breath sounds/wheezing, alopecia, erythema multiforme, and Stevens-Johnson syndrome.[22]

Drug and Food Interactions

Trizivir may be administered with or without food. Administration of Trizivir with food did not alter the extent of abacavir, lamivudine, and zidovudine area under the concentration-time curve (AUC), compared with administration under fasting conditions.[23]

Abacavir, lamivudine, and zidovudine (studied as individual drugs) are not significantly metabolized by the cytochrome P 450 enzymes; therefore, it is unlikely that clinically significant drug interactions

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Drug and Food Interactions (cont.)

will occur with drugs metabolized through these pathways.[24]

Abacavir administered at twice the recommended dose increased methadone clearance by 22%. A small number of patients receiving both abacavir and methadone may need a methadone dosage adjustment. Because abacavir elimination is decreased by alcohol, consumption of alcohol may cause an increase in abacavir exposure.[25]

Because lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another, Trizivir should not be coadministered with zalcitabine.[26] The AUC of lamivudine was increased by 43% and renal clearance was decreased by 30% when coadministered with sulfamethoxazole/trimethoprim. Concurrent administration of lamivudine and zidovudine in one small study resulted in a 39% increase in the C_{max} of zidovudine with no change observed in the AUC. Concurrent administration of lamivudine with indinavir and zidovudine resulted in a 6% decrease in the AUC of lamivudine, no change in the AUC of indinavir, and a 36% increase in the AUC of zidovudine. No adjustment in dose is necessary. Concurrent administration of lamivudine with drugs associated with pancreatitis (alcohol, didanosine, IV pentamidine, sulfonamides, and zalcitabine) or with drugs associated with peripheral neuropathy (dapson, didanosine, isoniazid, stavudine, and zalcitabine) should be avoided or used cautiously.[27]

Zidovudine may interact with atovaquone, fluconazole, methadone, probenecid, ribavirin, valproic acid,[28] nelfinavir, and ritonavir.[29] The hematologic toxicity of zidovudine may be increased when zidovudine is coadministered with bone marrow depressant agents such as ganciclovir or interferon alfa, blood dyscrasia-causing medications, cytotoxic agents, or radiation therapy.[30] [31] Medications that are metabolized by hepatic glucuronidation such as acetaminophen, aspirin, benzodiazepines, cimetidine, indomethacin, lorazepam, and oxazepam may in theory increase the risk of toxicity of zidovudine or the coadministered medication.[32] Antagonistic relationships between zidovudine and stavudine,

doxorubicin, and ribavirin have been reported in vitro. Concomitant use of zidovudine with any of these three drugs should be avoided.[33]

Results of in vitro studies indicate that ribavirin reduces the phosphorylation of pyrimidine nucleoside analogues, including lamivudine. Liver decompensation has occurred in patients coinfecting with HIV and hepatitis C virus receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin.[34]

Contraindications

Trizivir tablets are contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. Trizivir contains abacavir sulfate, which has been associated with fatal hypersensitivity reactions. An actual or suspected hypersensitivity reaction to abacavir sulfate is an absolute contraindication to Trizivir use.[35] Recent research has concluded that positivity for the HLA B*5701 genetic allele is a marker for abacavir hypersensitivity; patients who test positive for this variant are at risk for developing hypersensitivity reaction and should not receive abacavir.[36] [37] Due to the fixed-dose formulation of Trizivir, there is no way to accommodate the dosage reduction of zidovudine that may be necessary in individuals with impaired liver function or the dosage adjustment of both lamivudine and zidovudine that may be necessary in those with renal insufficiency (creatinine clearance less than 50 ml/min). Additionally, dosage adjustments cannot be made for pediatric or geriatric patients, for patients who weigh less than 40 kg, or for any patient who has special dosing requirements. Trizivir is not recommended for these patients.[38]

Clinical Trials

For information on clinical trials that involve Abacavir/Lamivudine/ Zidovudine, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Abacavir/Lamivudine/ Zidovudine AND HIV Infections.

Abacavir/Lamivudine/ Zidovudine



Dosing Information

Mode of Delivery: Oral.[39]

Dosage Form: Film-coated tablet containing abacavir sulfate 300 mg, lamivudine 150 mg, and zidovudine 300 mg.

The recommended dosage for adults and adolescents is one tablet twice daily. Because it is in a fixed-dose tablet, Trizivir is not recommended for use in adults or adolescents who weigh less than 40 kg (88 lbs) or in patients who require dosage adjustment, such as those who have creatinine clearance less than 50 ml/min or those who experience dose-limiting adverse events.[40]

Storage: Store at 25 C (77 F); excursions permitted to 15 C to 30 C (59 F to 86 F).[41]

Chemistry

CAS Name: Abacavir sulfate: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate[42]

Lamivudine: 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-, (2R-cis)-[43]

Zidovudine: Thymidine, 3'-azido-3'-deoxy-[44]

CAS Number: Abacavir sulfate: 188062-50-2[45]

Lamivudine: 134678-17-4[46]

Zidovudine: 30516-87-1[47]

Molecular formula: Abacavir sulfate: C₁₄H₁₈N₆O₁/2H₂O₄S; Lamivudine: C₈H₁₁N₃O₃S; Zidovudine: C₁₀H₁₃N₅O₄[48]

Abacavir sulfate: C50.1%, H5.7%, N25.1%, O14.3%, S4.8%; Lamivudine: C41.91%, H4.84%, N18.33%, O20.94%, S13.99%; Zidovudine: C44.94%, H4.90%, N26.21%, O23.95%[49]

Molecular weight: Abacavir sulfate: 670.76; Lamivudine: 229.26; Zidovudine: 267.24[50]

Melting point: Abacavir: 165 C; Lamivudine: 160

to 162 C; Zidovudine: 106 to 112 C[51]

Physical Description: Abacavir sulfate: white to off-white solid.[52]

Lamivudine: white to off-white crystalline solid.[53]

Zidovudine: white to beige crystalline solid.[54]

Solubility: Abacavir sulfate: 77 mg/ml in distilled water at 25 C.[55]

Lamivudine: 70 mg/ml in water at 20 C.[56]

Zidovudine: 20.1 mg/ml in water at 25 C.[57]

Other Names

Abacavir sulfate / Lamivudine / Zidovudine[58]

Further Reading

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Manufacturer Information

Abacavir/Lamivudine/ Zidovudine
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709
(888) 825-5249

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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