

Abacavir

Brand Name: Ziagen

Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Abacavir is a synthetic analogue of guanine, a naturally occurring purine nucleoside. It differs structurally from other reverse transcriptase inhibitors (didanosine, lamivudine, stavudine, zalcitabine, and zidovudine) in that it is a carbocyclic nucleoside analogue rather than a dideoxynucleoside analogue. [1]

HIV/AIDS-Related Uses

Abacavir sulfate was approved by the FDA on December 17, 1998, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children.[2] A patient's medical history should be reviewed for prior exposure to any abacavir-containing product before abacavir sulfate is administered in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.[3]

Abacavir is used in conjunction with other antiretroviral agents for postexposure prophylaxis of HIV infection in health care workers and other individuals exposed occupationally via percutaneous injury or mucous membrane or nonintact skin contact with blood, tissues, or other body fluids associated with a risk for HIV transmission.[4]

Pharmacology

Abacavir is a carbocyclic nucleoside analogue. It is converted by cellular enzymes to the active metabolite, carbovir triphosphate. An analogue of deoxyguanosine-5'-triphosphate (dGTP), carbovir triphosphate inhibits HIV-1 reverse transcriptase (RT) by competing with the natural substrate dGTP for incorporation into viral DNA. Once incorporated, carbovir triphosphate causes premature termination of viral DNA synthesis, because the incorporated nucleoside analogue lacks a 3'-OH group, thus preventing formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation. Abacavir is a weak inhibitor of cellular DNA polymerases alpha, beta, and gamma.[5] Abacavir is active in vitro against HIV-1 and -2.[6]

Abacavir sulfate is well absorbed following oral administration. Absorption is rapid and extensive. Abacavir sulfate has an absolute bioavailability of approximately 83%, which is not affected by food. After oral administration of 300 mg twice daily, the mean steady-state peak serum abacavir concentration (C_{max}) was 3.0 +/- 0.89 mcg/ml, and the area under the concentration-time curve (AUC) was 6.02 +/- 1.73 mcg(hour)/ml. After oral administration of a single 600 mg dose, the C_{max} was 4.26 +/- 1.19 mcg/ml, and the AUC was 11.95 +/- 2.5 mcg(hour)/ml. Systemic absorption is comparable following administration of tablets and oral solution.[7]

Following IV administration of abacavir sulfate, the apparent volume of distribution is 0.86 +/- 0.15 L/kg, suggesting distribution into extravascular spaces. Abacavir is distributed into cerebrospinal fluid (CSF). The steady-state CSF-to-plasma AUC ranges from 27% to 33%. Abacavir also readily distributes into erythrocytes. Plasma protein binding is approximately 50% and is independent of drug concentration.[8]

Abacavir is metabolized in the liver by alcohol dehydrogenase and glucuronyl transferase to form the metabolites 5'-carboxylic acid and 5'-glucuronide, neither of which has antiviral activity. Involvement of cytochrome P450 isoenzymes in metabolizing abacavir is limited. Following oral administration of a 600 mg dose of radiolabeled abacavir, 82.2% of the dose is excreted in urine and 16% is excreted as feces, with unchanged abacavir accounting for 1.2% of recovered radioactivity in urine. The elimination half-life following a single dose is approximately 1.5 hours.[9] It is unknown whether abacavir is removable by hemodialysis or peritoneal dialysis.[10]

Abacavir sulfate is in FDA Pregnancy Category C. No adequate or well-controlled studies of abacavir have been done in pregnant women. Studies in laboratory animals have shown that abacavir crosses the placenta, with evidence of fetal toxicity at dosage levels many times higher than the corresponding dosage for humans. Abacavir should be used in pregnancy only if the potential benefits

Pharmacology (cont.)

outweigh the risks. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to abacavir and other antiretroviral agents. Physicians may register patients by calling 1-800-258-4263 or online at <http://www.APRegistry.com>. It is not known whether abacavir is excreted in human milk; it is excreted in the milk of laboratory animals. Because of the potential for HIV transmission and for serious adverse effects from abacavir to the breastfed infant, women should be instructed not to breastfeed while taking abacavir.[11]

In ACTG 5202, a Phase IIIb study in 515 HLA-B*5701--negative patients, abacavir plus lamivudine combined with ritonavir-boosted atazanvir was evaluated as part of initial treatment regimens. At Week 36 analysis, 80% experienced virologic suppression; in the subset of patients with high viral loads, 76% achieved virologic suppression. However, a 12-trial meta-analysis reported lower rates of suppression with protease inhibitor--based regimens that included abacavir plus lamivudine compared with tenofovir/emtricitabine.[12] [13] [14]

HIV-1 isolates with reduced sensitivity to abacavir have been selected in vitro and also have been obtained from patients treated with abacavir. Genetic analysis of isolates from abacavir-treated patients showed point mutations in the RT gene resulting in amino acid substitutions of K65R, L74V, Y115F, and M184V. The mutation M184V/I was the commonly observed mutation in virologic failure isolates from patients receiving abacavir. In vitro, abacavir has synergistic activity in combination with amprenavir, nevirapine, and zidovudine and additive activity in combination with didanosine, lamivudine, stavudine, and zalcitabine.[15]

Recombinant laboratory strains of HIV-1 containing multiple RT abacavir resistance mutations exhibited cross resistance to didanosine, emtricitabine, lamivudine, tenofovir disoproxil fumarate, and zalcitabine in vitro. An increasing number of thymidine analogue mutations (TAMs) are associated with a progressive reduction in abacavir susceptibility. There is evidence that HIV

isolates that are highly resistant to multiple dideoxynucleoside reverse transcriptase inhibitors have reduced susceptibility to abacavir.[16]

Cross resistance between abacavir and protease inhibitors (PIs) is unlikely because the drugs target different enzymes; cross resistance between abacavir and non-nucleoside reverse transcriptase inhibitors (NNRTIs) is also unlikely because of different binding sites and mechanisms of action.[17]

Adverse Events/Toxicity

Fatal hypersensitivity reactions have been associated with abacavir therapy. Patients who develop signs or symptoms of hypersensitivity (including fever; skin rash; fatigue; gastrointestinal symptoms, such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms, such as pharyngitis, dyspnea, or cough) should discontinue abacavir as soon as a hypersensitivity reaction is suspected. To avoid a delay in diagnosis and to minimize the risk of a life-threatening hypersensitivity reaction, abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications). Abacavir should not be restarted after a hypersensitivity reaction, because 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 reintroduction of abacavir in patients who have no identified history of unrecognized symptoms of hypersensitivity to abacavir therapy. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.[18]

In clinical studies, hypersensitivity reactions have been reported in approximately 8% of adult and pediatric patients receiving abacavir in conjunction with lamivudine and zidovudine. Hypersensitivity-related fatalities have also been reported with abacavir use. Hypersensitivity reactions are characterized by symptoms indicating involvement of multiple organ and body systems

Adverse Events/Toxicity (cont.)

and usually appear within the first 6 weeks of abacavir therapy, although they may appear at any time.[19] Signs and symptoms of hypersensitivity include skin rash or a combination of two or more of the following: fever; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as pharyngitis, dyspnea, and cough.[20] Other signs and symptoms include malaise, lethargy, myalgia, myolysis, headache, arthralgia, edema, paresthesia, lymphadenopathy, and mucous membrane lesions such as conjunctivitis and mouth ulcerations. Laboratory abnormalities indicating hypersensitivity reaction include lymphopenia and increases in serum concentrations of liver enzymes, creatine kinase, or creatinine. Anaphylaxis, liver failure, renal failure, hypotension, and death have occurred in association with hypersensitivity reactions.[21]

Recently, the genetic HLA B*5701 allele variant has been associated with an increased likelihood of abacavir hypersensitivity reaction. New research 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.[22] [23] Current recommendations from the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents are to administer genetic testing for the HLA B*5701 variant before beginning treatment (or re-treatment) with abacavir in HIV infected

patients. In addition, abacavir should be permanently discontinued in patients who experience hypersensitivity, and the reactions should be reported to the Abacavir Hypersensitivity Reaction Registry at 800-270-0425.[24] [25]

Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogues alone or in combination, including abacavir and other antiretroviral agents. These conditions are sometimes fatal. The majority of cases have occurred in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised in any patient who has known risk factors for liver disease; however, cases have been reported in patients with no known risk factors. Treatment with abacavir sulfate should be suspended in any patient who develops clinical or laboratory findings that suggest lactic acidosis or pronounced hepatotoxicity.[26]

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including abacavir. During the initial phase of combination antiretroviral treatment, a patient whose immune system improves may develop an inflammatory response to indolent or residual opportunistic infections, such as *Mycobacterium avium* infection, cytomegalovirus infections, *Pneumocystis jirovecii* pneumonia, or tuberculosis. Symptoms of immune reconstitution syndrome necessitate further evaluation and treatment.[27]

Redistribution of body fat, peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy.[28]

In a clinical trial performed in treatment-naive adults given abacavir, lamivudine, and zidovudine twice daily, the most common adverse effects observed were nausea, headache, malaise and fatigue, and vomiting.[29] In this clinical study, laboratory abnormalities (e.g., creatine phosphokinase elevations, liver function test [specifically, ALT] abnormalities, neutropenia) were observed with similar frequencies as in treatment-naive adults who received indinavir three times daily and lamivudine and zidovudine twice daily.[30]

Adverse Events/Toxicity (cont.)

In an ongoing study of more than 33,000 HIV-infected patients, recent use of abacavir and didanosine in multidrug regimens were linked to significant increases in the risk of myocardial infarction (MI; relative risks of 1.49 [P=0.003] and 1.90 [P=0.0001], respectively). The association was noted in patients who were most likely to develop future heart disease; the association remained even after analyses were adjusted for those patients; and the association did not increase with cumulative or long-term (greater than 6 months) use of the drugs. In 54 manufacturer-conducted trials of abacavir, no risk association was observed with abacavir use compared with placebo; however, these manufacturer results are considered inconclusive by the FDA. No mechanism of action has been identified for the increased risk of MI. Current recommendations are to continue abacavir use in patients who have a low to moderate risk of MI and to carefully consider use of abacavir in patients who are at high risk for MI.[31]

Drug and Food Interactions

Abacavir may be taken with or without food.[32]

Concurrent use of abacavir and ethanol or other alcohol-containing products may result in increased concentrations and an increased half-life of abacavir as a result of competition for common metabolic pathways via alcohol dehydrogenase.[33]

Concomitant use of abacavir and methadone resulted in a methadone clearance increase by 22% in patients stabilized on oral methadone maintenance therapy who started abacavir therapy with abacavir 600 mg twice daily. Increases in clearance may not be clinically significant in a majority of patients, but methadone dosage increases may be required in some patients.[34] [35]

In human liver microsomes, abacavir did not significantly inhibit cytochrome P450 isoforms 2C9, 2D6, or 3A4; therefore, clinically important interactions between abacavir and drugs metabolized through these pathways are not expected.[36]

Contraindications

Abacavir is contraindicated in patients with previously demonstrated hypersensitivity to abacavir sulfate or to any of the components of the products.[37] A Medication Guide and Warning Card summarizing the symptoms of abacavir hypersensitivity reactions should be dispensed by the pharmacist with each new prescription and refill of abacavir (or abacavir-containing products, such as Epzicom and Trizivir). Patients being treated with abacavir sulfate should carry the warning card with them.[38]

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. Hypersensitivity to abacavir is a multiorgan clinical syndrome usually characterized by a sign or symptom in two or more of the following groups: fever, rash, gastrointestinal problems (including nausea, vomiting, diarrhea, or abdominal pain), constitutional problems (including generalized malaise, fatigue, or achiness), and respiratory problems (including dyspnea, cough, or pharyngitis). Abacavir should not be restarted following a hypersensitivity reaction to abacavir, because more severe symptoms can occur within hours and may include life-threatening hypotension and death.[39] 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.[40] [41]

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir sulfate and other antiretroviral agents.[42]

Clinical Trials

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

Abacavir



Dosing Information

Mode of Delivery: Oral.[43]

Dosage Form: Film-coated tablets containing abacavir 300 mg.[44]

Oral solution containing abacavir 20 mg/ml.[45]

The recommended dose of abacavir for adults is 600 mg (300 mg twice daily or 600 mg once daily) in combination with other antiretroviral agents. The recommended dosage of abacavir in patients with mild hepatic impairment (Child-Pugh score 5-6) is 200 mg twice daily. The recommended dosage of abacavir for adolescents and pediatric patients age 3 months to 16 years is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents. To enable dose reduction, abacavir oral solution (10 ml twice daily) should be used for the treatment of these patients.[46]

Storage: Store tablets and oral solution at controlled room temperature of 20 C to 25 C (68 F to 77 F).[47]

Oral solution may be refrigerated but should not be frozen.[48]

Chemistry

CAS Name: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (1:1)[49]

CAS Number: 188062-50-2 (abacavir sulfate)[50]

Molecular formula: (C₁₄-H₁₈-N₆-O)₂-H₂SO₄[51]

C50.1%, H5.7%, N25.1%, O14.3%, S4.8%[52]

Molecular weight: 670.76 (abacavir sulfate)[53]

Melting point: 165 C[54]

Physical Description: Tablets: white to off-white solid.[55]

Oral solution: clear to opalescent, yellowish, strawberry-banana flavored liquid.[56]

Solubility: 77 mg/ml in distilled water at 25 C.[57]

Other Names

ABC sulfate[58]

ABC[59]

Abacavir sulfate[60]

Further Reading

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Manufacturer Information

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

Ziagen
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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