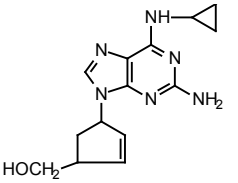
Abacavir

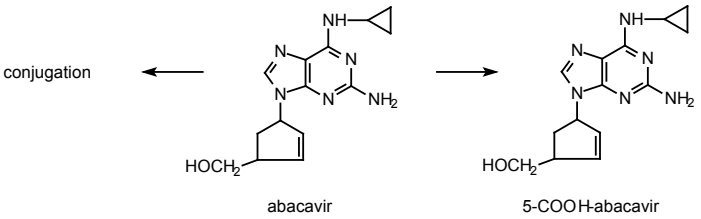
$t_{1/2}$: 0.9–3.7 h
Vd: 0.7–1.0 L/kg
Fb: 0.50
pKa: 5.0 (base)
b/p: 1.0
CAS: 136470-78-5
MW: 286.33 ($C_{14}H_{18}N_6O$)



Occurrence and Usage. Abacavir (Ziagen, ingredient of Epzicom, Kivexa, Trizivir) is a nucleoside analogue and reverse transcriptase inhibitor used in the treatment of HIV infections, often in combination with other antiviral agents, since 1998. It is available as the sulfate salt in 300–600 mg tablets and a 20 mg/mL solution for oral administration. It is also available in combination with lamivudine as a single tablet for once-daily dosing (Epzicom) and with lamivudine and zidovudine as a single tablet for twice-daily dosing (Trizivir). The recommended adult dose is 300 mg given twice daily or 600 mg once daily.

Blood Concentrations. A single oral 300 mg dose given to 18 adult HIV patients resulted in an average peak plasma abacavir concentration of 2.6 mg/L (range, 2.3–2.9) occurring at 0.4–1.1 hours and declining with an elimination half-life averaging 1.4 hours. The oral bioavailability of abacavir averages 83% (Chittick et al., 1999). A single oral 600 mg dose in 8 adult patients yielded an average peak plasma level of 4.7 mg/L at 1.7 hours, with a 1.7 hour elimination half-life (Kumar et al., 1999). Adult patients receiving twice-daily 300 mg oral doses for 12 weeks exhibited peak plasma levels averaging 3.0 mg/L (range, 2.4–3.7) at the end of the study (McDowell et al., 2000). Neither renal dysfunction (Izzedine et al., 2001) nor co-administration of lamivudine or zidovudine (Wang et al., 1999) was found to significantly alter the pharmacokinetics of abacavir.

Metabolism and Excretion. A single oral labeled abacavir dose is eliminated in the urine (83%) and feces (16%) over a 10 day period. Urinary elimination products include the 5'-glucuronide conjugate (36% of a dose), 5'-COOH-abacavir (30%) and unchanged drug (1.9%). None of the known metabolites has significant pharmacologic activity (Chittick et al., 1999; McDowell et al., 1999; PDR, 2001).



Toxicity. The adverse effects associated with abacavir therapy include nausea, vomiting, diarrhea, loss of appetite and insomnia. A hypersensitivity syndrome, potentially fatal, has been described that is often manifested by fatigue, myalgia, fever, dyspnea, headache, edema, paresthesia and skin rash. Genetic screening for the HLA-B*5701 allele, present in 6% of the population, has been recommended to preclude use of the drug in susceptible persons (Mallal et al., 2008). Two young women developed reversible hepatitis within 1–3 months of beginning therapy (Soni et al., 2008). A 47 year old man exhibited manic behavior one week after initiation of therapy with the drug (Brouilette and Routy, 2007). Anaphylaxis has occurred after temporary interruption of therapy, and at least one case of agranulocytosis has been described (Tikhomirov et al., 1999; Walensky et al., 1999; Frissen et al., 2001).

Analysis. Abacavir has been determined in biological fluids by liquid chromatography with ultraviolet (Veldkamp et al., 1999; Ravitch and Moseley, 2001; Sparidans et al., 2001; Ferrer et al., 2004) or mass spectrometric detection (Le Saux et al., 2008; Yadav et al., 2010).

Abacavir was stable in plasma for 4.5 hours at 60 °C (heat inactivation), 3 days at room temperature (Veldkamp et al., 1999) and 11 months at -20 or -80 °C (Sparidans et al., 2001). It was stable in urine for 5 hours at 58 °C and 6 weeks at -20 °C (Ravitch asnd Moseley, 2001).

References

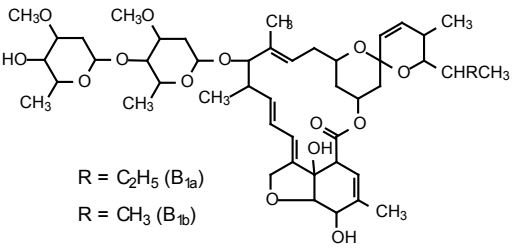
M.J. Brouilette and J.P. Routy. Abacavir sulfate and mania in HIV. Am. J. Psychiat. 164: 979–980, 2007.

G.E. Chittick, C. Gillotin, J.A. McDowell et al. Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food. Pharmacotherapy 19: 932–942, 1999.

S.M. Ferrer, P. Modamio, C.F. Lastra and E.L. Marino. Determination of abacavir in human plasma by high-performance liquid chromatography with ultraviolet detection and the analytical error function. Biomed. Chrom. 18: 862–865, 2004.

P.H.J. Frissen, J. de Vries, H.M. Weigel and K. Brinkman. Severe anaphylactic shock after rechallenge with abacavir without preceding hypersensitivity. AIDS 15: 289–292, 2001.
H. Izzedine, V. Launay-Vacher, G. Aymard et al. Pharmacokinetics of abacavir in HIV-1-infected patients with impaired renal function. Nephron 89: 62–67, 2001.
P.N. Kumar, D.E. Sweet, J.A. McDowell et al. Safety and pharmacokinetics of abacavir (1592U89) following oral administration of escalating single doses in human immunodeficiency virus type 1-infected adults. Antimicrob. Agents Chemother. 43: 603–608, 1999.
T. Le Saux, S. Chhun, R. Rey et al. Quantification of seven nucleoside/nucleotide reverse transcriptase inhibitors in human plasma by high-performance liquid chromatography with tandem mass spectrometry. J. Chrom. B. 865: 81–90, 2008.
S. Mallal, E. Phillips, G. Carosi et al. HLA-B*5701 screening for hypersensitivity to abacavir. New Eng. J. Med. 358: 568–579, 2008.
J.A. McDowell, G.E. Chittick, J.R. Ravitch et al. Pharmacokinetics of (^{14}C)abacavir, a human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitor, administered in a single oral dose to HIV-1-infected adults: a mass balance study. Antimicrob. Agents Chemother. 43: 2855–2861, 1999.
J.A. McDowell, Y. Lou, W.S. Symonds and D.S. Stein. Multiple-dose pharmacokinetics and pharmacodynamics of abacavir alone and in combination with zidovudine in human immunodeficiency virus-infected adults. Antimicrob. Agents Chemother. 44: 2061–2067, 2000.
Physicians' Desk Reference, Medical Economics Company, Montvale, New Jersey, 2001.
J.R. Ravitch and C.G. Moseley. High-performance liquid chromatographic assay for abacavir and its two major metabolites in human urine and cerebrospinal fluid. J. Chrom. B 762: 165–173, 2001.
S. Soni, D.R. Churchill and Y. Gilleece. Abacavir-induced hepatotoxicity: a report of two cases. AIDS 22: 2557–2558, 2008.
R.W. Sparidans, R.M.W. Hoetelmans and J.H. Beijnen. Liquid chromatographic assay for simultaneous determination of abacavir and mycophenolic acid in human plasma using dual spectrophotometric detection. J. Chrom. B 750: 155–161, 2001.
V. Tikhomirov, K. Namek and R. Hindes. Agranulocytosis induced by abacavir. AIDS 13: 1420–1421, 1999.
A.I. Veldkamp, R.W. Sparidans, R.M.W. Hoetelmans and J.H. Beijnen. Quantitative determination of abacavir (1592U89), a novel nucleoside reverse transcriptase inhibitor, in human plasma using isocratic reversed-phase high-performance liquid chromatography with ultraviolet detection. J. Chrom. B 736: 123–128, 1999.
R.P. Walensky, J.H. Goldberg and J.P. Daily. Anaphylaxis after rechallenge with abacavir. AIDS 13: 999–1000, 1999.
L.H. Wang, G.E. Chittick and J.A. McDowell. Single-dose pharmacokinetics and safety of abacavir (1592U89), zidovudine, and lamivudine administered alone and in combination in adults with human immunodeficiency virus infection. Antimicrob. Agents Chemother. 43: 1708–1715, 1999.
M. Yadav, A. Gupta, P. Singhal and P.S. Shrivastav. Development and validation of a selective and rapid LC-MS-MS method for the quantification of abacavir in human plasma. J. Chrom. Sci. 48: 654–662, 2010.

Abamectin



$t_{1/2}$: 2–3 days (subcutaneously in cattle)
5–6 days (orally in horses)
Vd: 1.0–1.5 L/kg (deer)
Fb: ?
b/p: ?
CAS: 71751-41-2
MW: 873.1 ($C_{48}H_{72}O_{14}$)

Occurrence and Usage. Abamectin (avermectin B_1, Abba, Affirm, Avid, Zephyr) is an antimicrobial substance, produced by *Streptomyces avermitilis*, that has been used since 1980 as an insecticide and veterinary anthelmintic agent. It is supplied as the neutral substance, a mixture of at least 80% abamectin B_{1b} and 20% or less abamectin B_{1a}, in a 0.01% bait or spray, 0.5% solution, 2% concentrate and 46–92% technical chemical for insecticidal purposes and in a 5 mg/mL topical solution, 80 mg extended-release oral capsule or a 1% injectable solution for administration to large animals.

Blood Concentrations. Blood or plasma levels of abamectin have not been determined in exposed, asymptomatic humans. A single oral 0.2 mg/kg dose in horses led to an average peak plasma abamectin concentration of 35 µg/L after 1.5 days, declining with a 5.6 day elimination half-life (Echeverria et al., 2001). A single subcutaneous 0.25 mg/kg dose in cattle produced an average peak plasma level of 54 µg/L after 3.0 days, with a 2.8 day elimination half-life (Borges et al., 2007). A single subcutaneous 0.2 mg/kg dose in deer yielded a peak plasma level that averaged 110 µg/L at 20 hours; the elimination half-life averaged 5.0 days (Zele et al., 2011).

Metabolism and Excretion. A single oral labeled abamectin dose in rats was eliminated over 7 days in urine (0.4% of the dose) and feces (94%). Biotransformation occurred via hydroxymethyl formation or O-demethylation, resulting in two minor metabolites (FAO, 1992). Very similar results were obtained in goats (Maynard et al., 1989).