Selected Properties of Abacavir

Other names	Ziagen®, ABC, 1592U89 Combination formulations: • Trizivir®: zidovudine + lamivudine + abacavir • Kivexa®: abacavir + 3TC (Epzicom® in USA) • Triumeq®: abacavir/dolutegravir/lamivudine
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	• Carbocyclic nucleoside analog. • Activated intracellularly to triphosphate derivative carbocyclic guanine analog which inhibits HIV reverse transcriptase. • In vitro studies have shown that abacavir exhibits marked synergy with AZT, amprenavir, nevirapine • Additive activity with ddI, ddC, 3TC
Activity	IC50 = 0.26 - 4.0 uM depending on cell type (MT-4 cells, PBMC's or macrophages) and HIV-1 source
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • K65R, L74V, Y115F, M184V* Requires multiple mutations in HIV-1 RT to confer modest (10 fold) reductions in abacavir susceptibility. **M184 alone is not associated with reduced response to abacavir; when present with 2 or more TAMS, M184V contributes to reduced susceptibility to abacavir* • *Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E* • *69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.* • *Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): K65R: 2.6-fold ↑ (intermediate resistance) K65R + M184V: 10-fold ↑ (high resistance) L74V: 2.1-fold ↑ (low resistance) L74V + M184V: 5.7-fold ↑ (high resistance) Y115F + M184V: 9.8-fold ↑ (high resistance) M184V: 3.3-fold ↑ (intermediate resistance) M184V + TAMS: 5-9-fold ↑ (high resistance)

Cross-Resistance	• Minimal (1-4 fold ↑ IC_{50}) cross-resistance with other RTIs: • AZT resistant strain: 2-fold ↑ IC_{50} of abacavir • 3TC resistant strain: 2.2 fold ↑ IC_{50} of abacavir • ddI, ddC resistant strains (2-10 fold ↑ IC_{50}); 2.2 fold↑ IC_{50} of abacavir • many NNRTI resistant strains (>1000 fold ↑ IC_{50}); 1.3-fold↑ IC_{50} of abacavir
Oral Bioavailability	83% (adults)
Effect of Food	Food delays absorption and decreases abacavir Cmax but does not affect overall plasma concentrations (AUC). Therefore abacavir can be taken with or without food.
Protein Binding	50%
Vd	
Tmax	1.5 hours (tablet), 1 hour (oral solution)
Serum T ½	1 - 1.3 hours
Intracellular T½	3.3 hours
Drug Concentrations	AUC and Cmax increase linearly with dose. At therapeutic dosages (300mg twice daily), the steady state Cmax of abacavir tablets is ~ 3 ug/mL, and the AUC over a dosing interval of 12 hours is approximately 6 ug.h/ml. The Cmax value for the oral solution is slightly higher than the tablet. There is no difference in AUC between tablets and solution. In pediatric patients, the pharmacokinetics of abacavir have been have been studied after either single or repeat dosing. Following multiple-dose administration of ZIAGEN 8 mg/kg twice daily, steady-state AUC $_{(0\text{-}12\ hr)}$ and Cmax were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively.
CSF (% of serum)	18% (N=4). Mean CSF concentrations 0.5 uM (approx. twice IC_{50} of 0.26 uM). The distribution of abacavir into CSF was assessed by use of a population pharmacokinetics analysis. Plasma and CSF abacavir concentrations in 54 subjects were determined. The abacavir CSF/plasma ratio averaged 36% and increased throughout the dose interval.[Capparelli E et al. 2005] In 10 HIV-infected subjects on ABC/FPV regimens with matched CSF & plasma samples, ABC concentrations were similar in CSF & plasma, with a median CSF:IC50 ratio 0.98 (IQR 0.29-1.59). 50% of abacavir CSF concentrations were >IC50wt (458 ng/mL).[Letendre S et al. 2009] 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	Alcohol dehydrogenase and glucoronidation pathways.
Excretion	3% excreted in urine over 24 hour period after single dose study

<table>
<tr><td>Dosing – Adult</td><td>Ziagen®: 300 mg po BID; 600 mg po once daily; take with or without food

Trizivir®: 1 tablet po BID (abacavir 300 mg + zidovudine 300 mg + 3TC 150mg BID)
Kivexa®: 1 tablet po daily (abacavir 600 mg + 3TC 300 mg QD)

<u>Triumeq®:</u>
1 tablet daily (abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg) with or without food (treatment-naïve or treatment experienced INSTI-naïve only)</td></tr>
<tr><td>Dosing – Pediatric</td><td>1-3 months: 8 mg/kg BID (investigational)
Pediatrics (three months to 12 years of age): 8 mg/kg BID (maximum 300 mg BID)

For pediatric patients weighing more than 14 kg and who can swallow tablets, the dosing regimen using the scored 300 mg tablet is as follows:
<table>
<tr><th rowspan="2">Weight (kg)</th><th colspan="2">Dosage Regimen Using Scored Tablet</th><th rowspan="2">Total Daily Dose</th></tr>
<tr><th>AM Dose</th><th>PM Dose</th></tr>
<tr><td>14 to 21</td><td>½ tablet (150 mg)</td><td>½ tablet (150 mg)</td><td>300 mg</td></tr>
<tr><td>>21 to <30</td><td>½ tablet (150 mg)</td><td>1 tablet (300 mg)</td><td>450 mg</td></tr>
<tr><td><u>≥</u> 30</td><td>1 tablet (300 mg)</td><td>1 tablet (300 mg)</td><td>600 mg</td></tr>
</table></td></tr>
<tr><td>Special instructions for pediatric patients</td><td>20mg/mL oral solution available
- watch for rash and other hypersensitivity symptoms
- company provides hypersensitivity warning card for patient</td></tr>
</table>

Adjust in Liver Dysfunction	In subjects with mild hepatic impairment and confirmed cirrhosis (Child-Pugh score 5-6), there was a mean 1.89-fold ↑ in abacavir AUC, and 1.58 fold ↑ in half-life. The rates of formation & elimination of abacavir metabolites were ↓ , but overall AUCs were not affected. In patients (n=9) with moderate cirrhosis (Child-Pugh score 5-6), abacavir AUC ↑ by 89%, t1/2 ↑ by 58% compared to healthy controls [Raffi et al. 2000] May consider using reduced abacavir dose (e.g., 150 mg BID) in patients with moderate hepatic impairment with cirrhosis, although the Ziagen® product monograph states that abacavir is contraindicated in patients with moderate or severe hepatic impairment.
Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: (140 - age) (wt) x 60 (Scr) (50) *CrCl (mL/min) for women: as above multiplied by 0.85	Dosage adjustment is likely not necessary in renal dysfunction. Data from a single-dose pharmacokinetic study of abacavir ESRD patients (n=6) showed abacavir concentrations similar to those observed in normal renal function. The two major metabolites (5' - glucuronide and 5' -carboxylate metabolites) are likely to accumulate but are considered inactive. No dosing modification of abacavir is recommended in patients with renal dysfunction. However, abacavir should be avoided in patients with end-stage renal disease. Hemodialysis: abacavir may be administered without regard to dialysis schedule.

Toxicity	**HLA-B*5701 genetic screening is recommended prior to use of abacavir. If the test is positive for this allele, avoid use of abacavir.** Nausea, vomiting, fever, diarrhea, anorexia, headache, asthenia, and rash*. Headache, nausea, persistent blood and protein in urine. *NB: 5% incidence **potentially fatal hypersensitivity**. Onset 3-42 days (median 9 days). Sx include nausea, vomiting, malaise, fatigue, diarrhea, abdominal pain, fever, dyspnea +/- morbiliform eruption (rash not always present). Physical findings include lymphadenopathy, ulceration of mucous membranes. Labs: elevated LFTs, CK, creatinine and lymphopenia. Symptoms worsen with each dose if drug is continued. Symptoms resolve 1-2 days after drug D/C; **do NOT rechallenge** (hypotension, hospitalizations,death reported). **Ziagen® Support Line: 1-800-868-8898.** Lactic acidosis with severe hepatomegaly with steatosis reported (less likely than with ddI, d4T or AZT).
Pregnancy & Lactation	There are no adequate and well-controlled studies of abacavir use in pregnant women. To monitor maternal-fetal outcomes of pregnant women exposed to abacavir, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling GlaxoSmithKline's Drug Surveillance Department (1-800-387-7374). Abacavir and its metabolites are secreted into the milk of lactating rats. It is expected that these will also be secreted into human milk, although this has not been confirmed. There is no data available on the safety of abacavir when administered to babies less than three months old.
Drug Interactions	In vitro evidence: alcohol dehydrogenase has a role in the metabolism of abacavir. Abacavir could compete for metabolism with alcohol resulting in increased concentrations of either agent; however, interaction study showed no clinically significant effects of combination. Drugs with high plasma protein binding could compete with abacavir for binding sites resulting in increased free concentrations of either drug in plasma. However, this effect would likely be transient as are most protein plasma binding interactions. See separate drug interaction chart.
Baseline Assessment	**HLA-B*5701 genetic screening is recommended prior to use of abacavir. If the test is positive for this allele, avoid use of abacavir.** CBC/diff, electrolytes, anion gap, serum bicarbonate, LFTs

Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, LFTs q3-6mos Measure serum lactate if low serum bicarbonate or high anion gap and Sx of lactic acidosis. Prodromal Sx include: nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue. Rapidly progressive Sx: tachycardia, tachypnea, hyperventilation, dyspnea, muscular weakness, jaundice, mental status changes. May also progress to multi-organ failure (hepatic, pancreatitis, encephalopathy, respiratory) and death. **D/C drug**: hypersensitivity reaction, Sx of lactic acidosis, serum lactate > 5 mmol/L, LFTs >5xULN
Dosage Forms	**Ziagen®:** 300 mg coated tablets, DIN 02240357. 20 mg/mL oral solution (strawberry-banana flavour), 240 mL bottle, DIN 02240358. Oral solution contains sorbitol which may cause abdominal pain and diarrhea. Sorbitol is metabolised to fructose and is therefore unsuitable for patients who have hereditary fructose intolerance. **Trizivir®:** azidovudine 300 mg/lamivudine 150 mg/abacavir 300 mg tablet, DIN 02244757. **Kivexa®:** abacavir 600 mg/lamivudine 300 mg tablet, DIN 02269341. **Triumeq®:** abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg, DIN 02430932.
Storage	Tablets and oral solution can be stored at room temperature.

References:

Capparelli EV, Letendre SL, Ellis RJ, Patel P, Holland D, McCutchan JA. Population pharmacokinetics of abacavir in plasma and cerebrospinal fluid. Antimicrob Agents Chemother 2005;49:2504-2506.

ViiV Healthcare ULC. Ziagen® Product monograph. Montreal, QC. December 21, 2009.

Letendre S, Best B, Rossi S, Way L, Grant I, Ellis R, et al. Therapeutic amprenavir and abacavir concentrations in CSF from the same individuals [abstract P_18]. 10th International Workshop on Clinical Pharmacology of HIV Therapy. Amsterdam, the Netherlands, April 15-17, 2009.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Raffi F, Benhamou Y, Sereni D, Poynard T, Brunet-Francois C, Emmanuel A, et al. Pharmacokinetics of, and tolerability to, a single oral 600 mg dose of abacavir in HIV-positive subjects with or without liver disease [abstract 1630]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada, September 17-20, 2000.

Thompson M, Torres G, Enstrom T, Bohn H, Savia J, Weinberg W, et al. Single-dose plasma profiles of abacavir in HIV-1-infected individuals with renal failure [abstract 42278]. 12th World AIDS Conference. Geneva, Switzerland, June 28-July 3, 1998.