

### Selected Properties of Abacavir

<b>Other names</b>	Ziagen®, ABC, 1592U89 Combination formulations: <ul style="list-style-type: none"> <li>• Trizivir®: zidovudine + lamivudine + abacavir</li> <li>• Kivexa®: abacavir + 3TC (Epzicom® in USA)</li> </ul>
<b>Manufacturer</b>	ViiV Healthcare Shire Canada
<b>Pharmacology/Mechanism of Action</b>	<ul style="list-style-type: none"> <li>• Carbocyclic nucleoside analog.</li> <li>• Activated intracellularly to triphosphate derivative carbocyclic guanine analog which inhibits HIV reverse transcriptase.</li> <li>• In vitro studies have shown that abacavir exhibits marked synergy with AZT, amprenavir, nevirapine</li> <li>• Additive activity with ddI, ddC, 3TC</li> </ul>
<b>Activity</b>	IC50 = 0.26 - 4.0 uM depending on cell type (MT-4 cells, PBMC's or macrophages) and HIV-1 source
<b>Resistance - genotypic</b>	<p>Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations):</p> <ul style="list-style-type: none"> <li>• K65R, L74V, Y115F, M184V*</li> </ul> <p>Requires multiple mutations in HIV-1 RT to confer modest (10 fold) reductions in abacavir susceptibility<sup>3</sup>.</p> <p><i>*M184 alone is not associated with reduced response to abacavir; when present with 2 or more TAMS, M184V contributes to reduced susceptibility to abacavir</i></p> <ul style="list-style-type: none"> <li>• <i>Presence of TAMS confers cross-resistance: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E</i></li> <li>• <i>69 Insertion Complex is associated with resistance to all approved NRTIs when present with ≥1 TAM at codons 41, 210 or 215.</i></li> <li>• <i>Q151M complex (with A62V, V75I, F77L, F116Y) is associated with resistance to all approved NRTIs except for tenofovir.</i></li> </ul>
<b>Resistance - phenotypic</b>	<p>Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (<a href="http://hivdb.stanford.edu/">http://hivdb.stanford.edu/</a>):</p> <p>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)</p>
<b>Cross-Resistance</b>	<ul style="list-style-type: none"> <li>• Minimal (1-4 fold ↑ IC<sub>50</sub>) cross-resistance with other RTIs:</li> <li>• AZT resistant strain: 2-fold ↑ IC<sub>50</sub> of abacavir</li> <li>• 3TC resistant strain: 2.2 fold ↑ IC<sub>50</sub> of abacavir</li> <li>• ddI, ddC resistant strains (2-10 fold ↑ IC<sub>50</sub>); 2.2 fold ↑ IC<sub>50</sub> of abacavir</li> <li>• many NNRTI resistant strains (&gt;1000 fold ↑ IC<sub>50</sub>); 1.3-fold ↑ IC<sub>50</sub> of abacavir</li> </ul>

<b>Oral Bioavailability</b>	83% (adults)
<b>Effect of Food</b>	Food delays absorption and decreases abacavir Cmax but does not affect overall plasma concentrations (AUC). Therefore abacavir can be taken with or without food.
<b>Protein Binding</b>	50%
<b>Vd</b>	
<b>Tmax</b>	1.5 hours (tablet), 1 hour (oral solution)
<b>Serum T<sub>1/2</sub></b>	1 - 1.3 hours
<b>Intracellular T<sub>1/2</sub></b>	3.3 hours
<b>Drug Concentrations</b>	<p>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.</p> <p>In pediatric patients, the pharmacokinetics of abacavir have been studied after either single or repeat dosing. Following multiple-dose administration of ZIAGEN 8 mg/kg twice daily, steady-state AUC<sub>(0-12 hr)</sub> and Cmax were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively.</p>
<b>CSF (% of serum)</b>	<p>18% (N=4). Mean CSF concentrations 0.5 uM (approx. twice IC<sub>50</sub> of 0.26 uM).</p> <p>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]</p> <p>In 10 HIV-infected subjects on ABC/FPV regimens with matched CSF &amp; plasma samples, ABC concentrations were similar in CSF &amp; plasma, with a median CSF:IC<sub>50</sub> ratio 0.98 (IQR 0.29-1.59). 50% of abacavir CSF concentrations were &gt;IC<sub>50</sub>wt (458 ng/mL).[Letendre S et al. 2009]</p> <p>2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]</p>
<b>Metabolism</b>	Alcohol dehydrogenase and glucoronidation pathways.
<b>Excretion</b>	3% excreted in urine over 24 hour period after single dose study
<b>Dosing – Adult</b>	<p>Ziagen®: 300 mg po BID; 600 mg po once daily; take with or without food</p> <p>Trizivir®: 1 tablet po BID (abacavir 300 mg + zidovudine 300 mg + 3TC 150mg BID)</p> <p>Kivexa®: 1 tablet po daily (abacavir 600 mg + 3TC 300 mg QD)</p>

<p><b>Dosing – Pediatric</b></p>	<p><b>1-3 months:</b> 8 mg/kg BID (investigational)  <b>Pediatrics (three months to 12 years of age):</b> 8 mg/kg BID (maximum 300 mg BID)</p> <p>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:</p> <table border="1" data-bbox="708 415 1395 743"> <thead> <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> </thead> <tbody> <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>&gt;21 to &lt;30</td> <td>½ tablet (150 mg)</td> <td>1 tablet (300 mg)</td> <td>450 mg</td> </tr> <tr> <td>≥ 30</td> <td>1 tablet (300 mg)</td> <td>1 tablet (300 mg)</td> <td>600 mg</td> </tr> </tbody> </table>	Weight (kg)	Dosage Regimen Using Scored Tablet		Total Daily Dose	AM Dose	PM Dose	14 to 21	½ tablet (150 mg)	½ tablet (150 mg)	300 mg	>21 to <30	½ tablet (150 mg)	1 tablet (300 mg)	450 mg	≥ 30	1 tablet (300 mg)	1 tablet (300 mg)	600 mg
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<p><b>Special instructions for pediatric patients</b></p>	<p>20mg/mL oral solution available</p> <ul style="list-style-type: none"> <li>- watch for rash and other hypersensitivity symptoms</li> <li>- company provides hypersensitivity warning card for patient</li> </ul>																		
<p><b>Adjust in Liver Dysfunction</b></p>	<p>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 &amp; 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.</p>																		
<p><b>Adjust in Renal Failure/ Dialysis</b></p> <p><sup>a</sup> CrCl (mL/min) for men:  <math display="block">\frac{(140 - \text{age}) (\text{wt}) \times 60}{(\text{Scr}) (50)}</math></p> <p>*CrCl (mL/min) for women:  as above multiplied by 0.85</p>	<p>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.</p> <p>No dosing modification of abacavir is recommended in patients with renal dysfunction. However, abacavir should be avoided in patients with end-stage renal disease.</p> <p>Hemodialysis: abacavir may be administered without regard to dialysis schedule.</p>																		

<b>Toxicity</b>	<p>Nausea, vomiting, fever, diarrhea, anorexia, headache, asthenia, and rash*. Headache, nausea, persistent blood and protein in urine (2/15).</p> <p>*NB: 5% incidence <b>potentially fatal hypersensitivity</b>. Onset 3-42 days (median 9 days). Sx include nausea, vomiting, malaise, fatigue, diarrhea, abdominal pain, fever, dyspnea +/- morbilliform 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; <b>do NOT rechallenge</b> (hypotension, hospitalizations, death reported). <b>Ziagen Support Line: 1-800-868-8898</b>.</p> <p>Lactic acidosis with severe hepatomegaly with steatosis reported (less likely than with ddI, d4T or ATZ).</p>
<b>Pregnancy &amp; Lactation</b>	<p>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).</p> <p>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.</p>
<b>Drug Interactions</b>	<p>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.</p> <p>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.</p> <p>See separate drug interaction chart.</p>
<b>Baseline Assessment</b>	CBC/diff, electrolytes, anion gap, serum bicarbonate, LFTs
<b>Routine Labs</b>	<p>CBC/diff, electrolytes, anion gap, serum bicarbonate, LFTs q3-6mos</p> <p>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.</p> <p><b>D/C drug:</b> hypersensitivity reaction, Sx of lactic acidosis, serum lactate &gt; 5 mmol/L, LFTs &gt;5xULN</p>

<b>Dosage Forms</b>	<p>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.</p> <p><b>Trizivir®:</b> azidovudine 300 mg/lamivudine 150 mg/abacavir 300 mg tablet, DIN 02244757.  <b>Kivexa®:</b> abacavir 600 mg/lamivudine 300 mg tablet, DIN 02269341.</p>
<b>Storage</b>	Tablets and oral solution can be stored at room temperature.

**References:**

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