

### Selected Properties of Lamivudine

<b>Other names</b>	3TC®, <b>3-thiacytidine</b> ; <b>Epivir®</b> : 3TC (USA) Combination formulations: <ul style="list-style-type: none"> <li>• <b>Combivir®</b>: 3TC + zidovudine</li> <li>• <b>Trizivir®</b>: zidovudine + 3TC + abacavir</li> <li>• <b>Kivexa®</b>: abacavir + 3TC (Epzicom® in the USA)</li> </ul>
<b>Manufacturer</b>	ViiV Healthcare Shire Canada
<b>Pharmacology/Mechanism of Action</b>	<ul style="list-style-type: none"> <li>• Cytidine analogue, intracellular triphosphorylation to active form with preferential activity in resting cell</li> <li>• Predominant mechanism of action is DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription</li> <li>• Competes with natural nucleoside substrate for binding to active site of reverse transcriptase</li> </ul>
<b>Activity</b>	In vitro IC <sub>50</sub> = 2 nM - 15 uM Active vs HBV
<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, M184V/I</li> <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: 9.7-fold ↑ (intermediate resistance) M184V: 200-fold ↑ (high resistance) K65R + M184V: 300-fold ↑ (high resistance)</p>
<b>Cross-Resistance</b>	The clinical relevance of genotypic and phenotypic changes associated with lamivudine therapy has not been fully established. In some patients harbouring zidovudine-resistant virus, phenotypic sensitivity to zidovudine was restored after treatment with lamivudine.
<b>Oral Bioavailability</b>	86%; food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate) delays rate but not extent of absorption.
<b>Effect of Food</b>	Can take with or without food.
<b>Protein Binding</b>	<36%
<b>Vd</b>	1.3L/kg
<b>Tmax</b>	1-1.5h

<b>Serum T<sub>1/2</sub></b>	2-6h
<b>Intracellular T<sub>1/2</sub></b>	10-15h
<b>Drug Concentrations</b>	<p>After single 300 mg oral dose (adults): C<sub>max</sub> 2.6 ug/mL AUC 11 ug.hr/mL</p> <p>300 mg QD vs. 150 mg BID dosing yields: similar plasma and intracellular AUCs, lower C<sub>trough</sub> in both plasma (53% ↓) and intracellular</p> <p>Pharmacokinetics in children (Burger et al. 2006):</p> <ul style="list-style-type: none"> <li>• Kinetic study in 40 children ages 1.7-18 years (median 7.3 yrs) taking 3TC 4 mg/kg BID revealed significantly ↑Cl/kg and V<sub>d</sub>/kg in children 6 years and younger vs. those 7 years and up</li> <li>• Children under 7 years had 36% ↓ AUC and 40% ↓ C<sub>max</sub> of 3TC compared to older children; dosing on BSA may provide less variability in 3TC exposure</li> </ul>
<b>CSF (% of serum)</b>	10% 2010 CNS Penetration Effectiveness (CPE) Score: 2 [Letendre S et al. 2010]
<b>Metabolism</b>	trans-sulfoxide is only known metabolite
<b>Excretion</b>	<ul style="list-style-type: none"> <li>• 70% excreted unchanged; renal tubular secretion</li> <li>• renal clearance 280ml/min</li> </ul>
<b>Dosing – Adult</b>	<p>≥ 50 kg: 150 mg po bid or 300 mg po once daily &lt;50kg: 2mg/kg po bid</p> <p><b>Combination tablets</b> <b>Combivir®:</b> 300 mg zidovudine/150 mg lamivudine po BID <b>Trizivir®:</b> zidovudine 300 mg/lamivudine 150 mg/abacavir 300 mg po BID <b>Kivexa®:</b> abacavir 600 mg/lamivudine 300 mg po QD</p>
<b>Dosing – Pediatric</b>	<p><b>Neonate (&lt; 30 days):</b> 2 mg/kg/dose po bid</p> <p><b>Children (3mo-12yrs):</b> 4mg/kg po bid, max 150mg bid 10mg/mL oral solution available.</p>
<b>Special instructions for pediatric patients</b>	If 3TC upsets the stomach, take with food. May cut tablet in half (not scored) or crush.
<b>Adjust in Liver Dysfunction</b>	No adjustment required.

<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>- reduce dose based on CrCl<sup>a</sup>:</p> <p>&gt;50ml/min: 300 mg QD or 150mg BID  30-49mL/min: 150mg QD  15-29mL/min: 150mg loading dose, then 100mg QD  5-14 mL/min: 150 mg loading dose, then 50 mg QD  &lt;5 mL/min: 50mg loading dose, then 25mg QD</p> <p>In one series of HIV-subjects with end-stage renal disease (n=9), 150 mg 3TC daily was well tolerated, despite AUCs elevated by 5-fold compared to subjects with normal renal function. Therefore, a dosage of 25 mg daily may be sufficient for this population. Administer lamivudine after completion of dialysis sessions.</p>
<p><b>Toxicity</b></p>	<p>Usually very well tolerated; headache, diarrhea, nausea, , nasal symptoms , fatigue dizziness, neutropenia , ↑ LFTs</p> <p>rare: rash, pancreatitis in pediatrics, ↑ amylase, sweating, taste disturbances, anemia, neuropathy; lactic acidosis, mitochondrial toxicity reported, however 3TC has a low potential for this vs. ddI, d4T, ddC, AZT.</p> <p>Severe acute exacerbations of HBV have been reported in patients who have discontinued lamivudine. Monitor hepatic function closely for several months upon discontinuation.</p>
<p><b>Pregnancy &amp; Lactation</b></p>	<p>Pregnancy risk category C. ~100% placental transfer in humans. Use normal adult doses in pregnancy. Due to extensive experience and lack of evidence for teratogenicity, 3TC + AZT are recommended as the dual NRTI backbone of a regimen. Secreted in human breast milk at similar concentrations to those found in serum.</p>
<p><b>Drug Interactions</b></p>	<p><b>trimethoprim</b> increases 3TC AUC 40% (adjust 3TC if renal dysfunction, monitor for 3TC toxicity)</p> <p><b>3TC</b> and ddC compete for intracellular phosphorylation in vitro, both cytidine analogues, thus avoid combination. Similarly, avoid coadministration with emtricitabine.</p> <p>See separate Drug Interaction chart.</p>
<p><b>Baseline Assessment</b></p>	<p>CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, LFTs</p>
<p><b>Routine Labs</b></p>	<p>CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, 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> Sx of lactic acidosis, serum lactate &gt; 5 mmol/L, amylase &gt;200 (asymptomatic), pancreatitis, LFTs &gt;5xULN, ANC&lt; 0.5, painful neuropathy</p>

<b>Dosage Forms</b>	<p><b>Tablet:</b> 150mg (white, diamond-shaped); DIN 02192683 300mg (gray-blue, diamond-shaped); DIN 02247825</p> <p><b>Oral Solution:</b> 10mg/mL (240mL); DIN 02192691; strawberry-banana flavor</p> <p><b>Combination tablets:</b> <b>Combivir®:</b> 300 mg zidovudine/150 mg lamivudine; DIN 02239213 <b>Trizivir®:</b> zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg tablet; DIN 02244757. <b>Kivexa®:</b> abacavir 600 mg + 3TC 300 mg tablet; DIN 02269341.</p>
<b>Storage</b>	Store tabs and solution at room temperature.

**References:**

Burger D et al. Age-dependent pharmacokinetics of lamivudine in HIV-infected children [abstract 20]. Presented at the 7<sup>th</sup> International Workshop on Clinical Pharmacology of HIV Therapy, Lisbon, April 20-22<sup>nd</sup>, 2006.

GlaxoSmithKline Shire. 3TC® Product monograph. Mississauga, Ont.: May 9<sup>th</sup>, 2009.

Izzedine H, Launay-Vacher V, Deray G. Dosage of lamivudine in a haemodialysis patient. Nephron. 2000 Dec;86(4):553.

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]. 17<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.