Selected Properties of Lamivudine

Other names	3TC®, **3-thiacytidine; Epivir®**: 3TC (USA) Combination formulations: • **Combivir**®: 3TC + zidovudine • **Apo-Lamivudine-Zidovudine®**: 150/300 mg tablet • **Trizivir®:** zidovudine + 3TC + abacavir • **Kivexa®**: abacavir + 3TC (Epzicom® in the USA) • **Triumeq®:** abacavir/dolutegravir/lamivudine
Manufacturer	ViiV Healthcare ULC
Pharmacology/Mechanism of Action	• Cytidine analogue, intracellular triphosphorylation to active form with preferential activity in resting cell • Predominant mechanism of action is DNA chain termination via absence of 3'-hydroxyl group to inhibit HIV reverse transcription • Competes with natural nucleoside substrate for binding to active site of reverse transcriptase
Activity	In vitro IC_{50} = 2 nM - 15 uM Active vs HBV
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): • K65R, M184V/I • *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: 9.7-fold ↑ (intermediate resistance) M184V: 200-fold ↑ (high resistance) K65R + M184V: 300-fold ↑ (high resistance)
Cross-Resistance	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. Complete cross-resistance with emtricitabline (FTC).
Oral Bioavailability	86%; food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate) delays rate but not extent of absorption.
Effect of Food	Can take with or without food.

Protein Binding	<36%
Vd	1.3L/kg
Tmax	1-1.5h
Serum T ½	2-6h
Intracellular T½	10-15h
Drug Concentrations	After single 300 mg oral dose (adults): Cmax 2.6 ug/mL AUC 11 ug.hr/mL 300 mg QD vs. 150 mg BID dosing yields: similar plasma and intracellular AUCs, lower Ctrough in both plasma (53% ↓) and intracellular Pharmacokinetics in children (Burger et al. 2006): • 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 Vd/kg in children 6 years and younger vs. those 7 years and up • Children under 7 years had 36% ↓ AUC and 40% ↓ Cmax of 3TC compared to older children; dosing on BSA may provide less variability in 3TC exposure
CSF (% of serum)	10% 2010 CNS Penetration Effectiveness (CPE) Score: 2 [Letendre S et al. 2010]
Metabolism	trans-sulfoxide is only known metabolite
Excretion	• 70% excreted unchanged; renal tubular secretion • renal clearance 280ml/min
Dosing – Adult	**3TC®:** ≥ 50 kg: 150 mg po bid or 300 mg po once daily <50kg: 2mg/kg po bid **Combination tablets** **Combivir®:** 1 tablet (300 mg zidovudine/150 mg lamivudine) po twice daily **Trizivir®:** 1 tablet (zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg) po twice daily **Kivexa®:** 1 tablet (abacavir 600 mg/lamivudine 300 mg) po once daily **Triumeq®:** 1 tablet daily (abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg) with or without food (treatment-naïve or treatment experienced INSTI-naïve only)
Dosing – Pediatric	**Neonate** (< 30 days): 2 mg/kg/dose po bid **Children (**3mo-12yrs): 4mg/kg po bid, max 150mg bid 10mg/mL oral solution available.

Special instructions for pediatric patients	If 3TC upsets the stomach, take with food. May cut tablet in half (not scored) or crush.
Adjust in Liver Dysfunction	No adjustment required.
Adjust in Renal Failure/ Dialysis [a] CrCl (mL/min) for men: $\frac{(140 - age)\ (wt) \times 60}{(Scr)\ (50)}$ *CrCl (mL/min) for women: as above multiplied by 0.85	- reduce dose based on CrCl[a]: >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 <5 mL/min: 50mg loading dose, then 25mg QD 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.
Toxicity	Usually very well tolerated; headache, diarrhea, nausea, , nasal symptoms , fatigue dizziness, neutropenia , ↑ LFTs 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. Severe acute exacerbations of HBV have been reported in patients who have discontinued lamivudine. Monitor hepatic function closely for several months upon discontinuation.
Pregnancy & Lactation	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.
Drug Interactions	**trimethoprim** increases 3TC AUC 40% (adjust 3TC if renal dysfunction, monitor for 3TC toxicity) **3TC** and ddC compete for intracellular phosphorylation in vitro, both cytidine analogues, thus avoid combination. Similarly, avoid coadministration with emtricitabine. See separate Drug Interaction chart.
Baseline Assessment	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase, LFTs

Routine Labs	CBC/diff, electrolytes, anion gap, serum bicarbonate, amylase/lipase, 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**: Sx of lactic acidosis, serum lactate > 5 mmol/L, amylase >200 (asymptomatic), pancreatitis, LFTs >5xULN, ANC< 0.5, painful neuropathy
Dosage Forms	**Tablet:** 3TC® 150mg (white, diamond-shaped); DIN 02192683 3TC® 300mg (gray-blue, diamond-shaped); DIN 02247825 Apo-Lamivudine® 150 mg tablet: 02369052 Apo-Lamivudine® 300 mg tablet: 02369060 **Oral Solution:** 10mg/mL (240mL); DIN 02192691; strawberry-banana flavor **Combination tablets:** **Combivir®:** 300 mg zidovudine/150 mg lamivudine; DIN 02239213 **Apo-Lamivudine-Zidovudine®**: 150/300 mg tablet, DIN 02375540 **Trizivir®:** zidovudine 300 mg/lamivudine150 mg/abacavir 300 mg tablet; DIN 02244757. **Kivexa®:** abacavir 600 mg + 3TC 300 mg tablet; DIN 02269341. **Triumeq®:** abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg; DIN 02430932.
Storage	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 7th International Workshop on Clinical Pharmacology of HIV Therapy, Lisbon, April 20-22nd, 2006.

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