Selected Properties of Emtricitabine

Other names	Emtriva®: FTC Combination formulations: **Truvada®:** emtricitabine/tenofovir **Atripla®:** efavirenz/emtricitabine/tenofovir **Complera®:** rilpivirine/emtricitabine/tenofovir **Stribild®:** elvitegravir/cobicistat/emtricitabine/tenofovir
Manufacturer	Gilead Sciences Canada, Inc.
Pharmacology/Mechanism of Action	• Cytosine 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	IC_{50} = 0.0013 – 0.64 uM (in vitro) Active against HBV, but not adequately studied for this indication.
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	Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine).
Oral Bioavailability	93% The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis.[Sandkovsky et al. 2012]

Effect of Food	No effect on AUC; 29% decrease in Cmax with approximately 1000 kcal high-fat meal.
Protein Binding	< 4% plasma proteins
Vd	
Tmax	1-2 hours
Serum T ½	10 hours
Intracellular T½	> 20 hours
Drug Concentrations	With steady-state dosing in adults, mean (±□SD) plasma concentrations were: Cmax 1.8 ±□0.7 µg/mL AUC 10.0 ±□3.1 hr*µg/mL Ctrough 0.09 µg/mL The multiple dose pharmacokinetics of emtricitabine are dose proportional over a dose range of 25 to 200 mg. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~ 1.0 and the mean semen to plasma drug concentration ratio was ~ 4.0. In children receiving a daily dose of 6 mg/kg up to a maximum of 240 mg oral solution or a 200 mg capsule, emtricitabine exposure was similar to exposures achieved in adults receiving a once-daily dose of 200 mg. In neonates <3 months of age, a daily dose of 3 mg/kg produces plasma levels similar to those achieved in pediatric patients (3 months-17 years) receiving 6 mg/kg/day [Blum et al. 2006]. In 34 HIV-infected pregnant women on tenofovir/emtricitabine-containing cART, emtricitabine exposures were ~25% lower in the 3rd trimester compared to post-partum; these results were independent of concomitant use of boosted PIs. The median (range) ratio of cord blood:maternal blood was 1.63 (0.46–1.82; N=10) for FTC.[Colbers et al. 2013]
CSF (% of serum)	2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	Not a substrate of CYP450 enzymes.
Excretion	86% urine (13% as metabolites); 14% feces; undergoes glomerular filtration and active tubular secretion

<table>
<tr><td>Dosing – Adult</td><td>Emtriva® (emtricitabine 200 mg): one tablet with or without food.
Truvada® (tenofovir 300 mg/emtricitabine 200 mg): one tablet once daily with or without food.
Complera® (emtricitabine 200 mg/rilpivirine 25 mg/tenofovir 300 mg): one tablet daily with a meal.
Atripla® (efavirenz 600 mg/tenofovir 300 mg/emtricitabine 200 mg): one tablet once daily preferably before bedtime. Can take with food, however high fat foods may increase the absorption by 50%, thus potentially increasing side effects.
Stribild®: (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir 300 mg): one table daily with food.</td></tr>
<tr><td>Dosing – Pediatric</td><td>Neonatal/Infant:
• Oral Solution: 3 mg/kg administered once daily orally.

Pediatric Patients (3 months through 17 years):
• Oral Solution: 6 mg/kg up to a maximum of 240 mg (24 mL) administered once daily orally.
• Capsules: for children weighing more than 33 kg who can swallow an intact capsule, one 200 mg capsule administered once daily orally.</td></tr>
<tr><td>Special instructions for pediatric patients</td><td></td></tr>
<tr><td>Adjust in Liver Dysfunction</td><td>No dosage adjustment is required.</td></tr>
<tr><td>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</td><td>In adult patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, Cmax and AUC of emtricitabine were increased. Reduce dose based on CrCl [a]:
<table>
<tr><th rowspan="2">Formulation</th><th colspan="4">Creatinine Clearance (mL/min)</th></tr>
<tr><th>≥50 mL/min</th><th>30–49 mL/min</th><th>15–29 mL/min</th><th><15 mL/min or on hemodialysis*</th></tr>
<tr><td>Capsule (200 mg)</td><td>200 mg every 24 hours</td><td>200 mg every 48 hours</td><td>200 mg every 72 hours</td><td>200 mg every 96 hours</td></tr>
<tr><td>Oral Solution (10 mg/mL)</td><td>240 mg every 24 hours (24 mL)</td><td>120 mg every 24 hours (12 mL)</td><td>80 mg every 24 hours (8 mL)</td><td>60 mg every 24 hours (6 mL)</td></tr>
</table>
* Hemodialysis Patients: If dosing on day of dialysis, give dose after dialysis.
Hemodialysis: 200 mg q 96 h, post-dialysis; 30% removed in 3-hour hemodialysis session</td></tr>
<tr><td>Toxicity</td><td>Usually very well tolerated. Headache, diarrhea, nausea, rash, skin discoloration (pigmentation of palms/soles mainly in non-Caucasian).
Lactic acidosis, mitochondrial toxicity reported.
Severe acute exacerbations of HBV have been reported in patients who have discontinued emtricitabine. Monitor hepatic function closely for several months upon discontinuation.</td></tr>
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Pregnancy & Lactation	Pregnancy risk category B. No studies in human pregnancy. Unknown if it is secreted into breast milk.
Drug Interactions	Potential for antagonism with 3TC or ddC, which are other cytidine analogues. Avoid coadministration. See separate Drug Interaction chart.
Baseline Assessment	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**: Sx of lactic acidosis, serum lactate > 5 mmol/L, LFTs >5xULN
Dosage Forms	**Emtriva®:** • 200 mg hard gelatin blue and white capsule, DIN 02272091 • 10 mg/mL oral solution (clear orange/dark orange), 170 mL bottle **Combination formulations:** • Truvada®: tenofovir 300 mg/emtricitabine 200 mg, DIN 02274906 • Atripla®: efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg tablet, DIN 02300699 • Complera®: Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir DF 300 mg tablet, DIN 02374129 • Stribild®: Elvitegravir 150 mg/cobicistat 150 mg/ emtricitabine 200 mg/ tenofovir DF 300 mg tablet
Storage	Store capsules at room temperature. Refrigerate oral solution at 2–8 °C (36–46 °F). Emtriva Oral Solution should be used within 3 months if stored by the patient at 25 °C (77 °F); excursions permitted to 15–30 °C (59–86 °F).

References:

Gilead Sciences Canada, Inc. Emtriva® Product monograph. Mississauga, Canada. March 13th, 2012.

Blum et al. Steady-state pharmacokinetic evaluation of emtricitabine in neonates exposed to HIV in utero [abstract 568]. Presented at the 13th Conference on Retroviruses and Opportunistic Infections, February 5-8, 2006, Denver, CO.

Colbers A, Hawkins DA, Gingelmaier A, et al. The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women. AIDS 2013; 27:739–748.

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.

Sandkovsky U, Swindells S, Moore R, Acosta EP, Fletcher CV. Acceptable plasma concentrations of raltegravir and etravirine when administered by gastrostomy tube in a patient with advanced multidrug-resistant human immunodeficiency virus infection. Pharmacotherapy 2012: 32(2):142–147.

