Emtriva®

(emtricitabine) Capsules

Emtriva

(emtricitabine) Oral Solution

℞ Only

WARNINGS

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

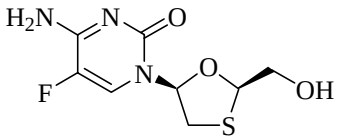
EMTRIVA IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF EMTRIVA HAVE NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRIVA. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE EMTRIVA AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

EMTRIVA® is the brand name of emtricitabine, a synthetic nucleoside analog with activity against human immunodeficiency virus type 1 (HIV-1) reverse transcriptase.

The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Emtricitabine is a white to off-white powder with a solubility of approximately 112 mg/mL in water at 25 °C. The log P for emtricitabine is -0.43 and the pKa is 2.65.

EMTRIVA is available as capsules or as an oral solution.

EMTRIVA Capsules are for oral administration. Each capsule contains 200 mg of emtricitabine and the inactive ingredients, crospovidone, magnesium stearate, microcrystalline cellulose, and povidone.

EMTRIVA Oral Solution is for oral administration. One milliliter (1 mL) of EMTRIVA Oral Solution contains 10 mg of emtricitabine in an aqueous solution with the following inactive ingredients: cotton candy flavor, FD&C yellow No. 6, edetate disodium, methylparaben, and propylparaben (added as preservatives), sodium phosphate (monobasic), propylene glycol, water, and xylitol (added as a sweetener). Sodium hydroxide and hydrochloric acid may be used to adjust pH.

MICROBIOLOGY

Mechanism of Action:

Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε, and mitochondrial DNA polymerase γ.

Antiviral Activity:

The antiviral activity in cell culture of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) value for emtricitabine was in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 μM).

Resistance:

Emtricitabine–resistant isolates of HIV have been selected in cell culture and in vivo. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I) mutations in the HIV reverse transcriptase gene.

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study of treatment-naive patients treated with EMTRIVA, didanosine, and efavirenz (Study 301A, see **Description of Clinical Studies**), viral isolates from 37.5% of patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene.

In a clinical study of treatment-naive patients treated with either EMTRIVA, VIREAD®, and efavirenz or zidovudine/lamivudine and efavirenz (Study 934, see **Description of Clinical Studies**), resistance analysis was performed on HIV isolates from all virologic failure patients with >400 copies/mL of HIV-1 RNA at Week 48 or early discontinuations. Development of efavirenz resistance-associated mutations occurred most frequently and was similar between the treatment arms. The M184V amino acid substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/12 (17%) analyzed patient isolates in the EMTRIVA + VIREAD group and in 7/22 (32%) analyzed patient isolates in the lamivudine/zidovudine group. Through 48 weeks of Study 934, no patients have developed a detectable K65R mutation in their HIV as analyzed through standard genotypic analysis. Insufficient data are available to assess the development of the K65R mutation upon prolonged exposure to this regimen.

Cross Resistance:

Cross-resistance among certain nucleoside analog reverse transcriptase inhibitors has been recognized. Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity in cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

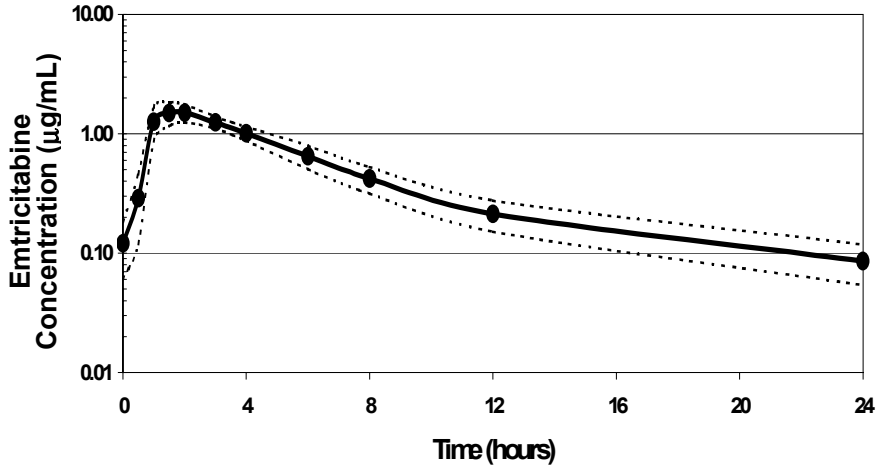
The in vivo activity of emtricitabine was evaluated in two clinical trials in which 101 patients were administered 25–400 mg a day of EMTRIVA as monotherapy for 10–14 days. A dose-related antiviral effect was observed, with a median decrease from baseline in plasma HIV-1 RNA of 1.3 $\log_{10}$ at a dose of 25 mg QD and 1.7 $\log_{10}$ to 1.9 $\log_{10}$ at a dose of 200 mg QD or BID.

Pharmacokinetics in Adults:

The pharmacokinetics of emtricitabine were evaluated in healthy volunteers and HIV-infected individuals. Emtricitabine pharmacokinetics are similar between these populations.

Figure 1 shows the mean steady-state plasma emtricitabine concentration-time profile in 20 HIV-infected subjects receiving EMTRIVA Capsules.

Figure 1 Mean (± 95% CI) Steady-State Plasma Emtricitabine Concentrations in HIV-Infected Adults (N=20)



Absorption:

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1–2 hours post-dose. Following multiple dose oral administration of EMTRIVA Capsules to 20 HIV-infected subjects, the (mean ± SD) steady-state plasma emtricitabine peak concentration (C_{max}) was 1.8 ± 0.7 μg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 hr•μg/mL. The mean steady state plasma trough concentration at 24 hours post-dose was 0.09 μg/mL. The mean absolute bioavailability of EMTRIVA Capsules was 93% while the mean absolute bioavailability of EMTRIVA Oral Solution was 75%. The relative bioavailability of EMTRIVA Oral Solution was approximately 80% of EMTRIVA Capsules.

The multiple dose pharmacokinetics of emtricitabine are dose proportional over a dose range of 25–200 mg.

Effects of Food on Oral Absorption:

EMTRIVA Capsules and Oral Solution may be taken with or without food. Emtricitabine systemic exposure (AUC) was unaffected while C_{max} decreased by 29% when EMTRIVA Capsules were administered with food (an approximately 1000 kcal high-fat meal). Emtricitabine systemic exposure (AUC) and C_{max} were unaffected when 200 mg EMTRIVA Oral Solution was administered with either a high-fat or low-fat meal.

Distribution:

In vitro binding of emtricitabine to human plasma proteins was <4% and independent of concentration over the range of 0.02–200 μg/mL. 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.

Metabolism:

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of ^{14}C-emtricitabine, complete recovery of the

dose was achieved in urine (~86%) and feces (~14%). Thirteen percent (13%) of the dose was recovered in urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

Elimination:

The plasma emtricitabine half-life is approximately 10 hours. The renal clearance of emtricitabine is greater than the estimated creatinine clearance, suggesting elimination by both glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations:

Race, Gender and Elderly

The pharmacokinetics of emtricitabine were similar in adult male and female patients and no pharmacokinetic differences due to race have been identified.

The pharmacokinetics of emtricitabine have not been fully evaluated in the elderly.

Hepatic Impairment

The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment, however, emtricitabine is not metabolized by liver enzymes, so the impact of liver impairment should be limited.

Pediatrics

The pharmacokinetics of emtricitabine at steady state were determined in 77 HIV-infected children, and the pharmacokinetic profile was characterized in four age groups (Table 1). The emtricitabine exposure achieved in children receiving a daily dose of 6 mg/kg up to a maximum of 240 mg oral solution or a 200 mg capsule is similar to exposures achieved in adults receiving a once-daily dose of 200 mg.

The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV-positive mothers. Each mother received prenatal and intrapartum combination antiretroviral therapy. Neonates received up to 6 weeks of zidovudine prophylactically after birth. The neonates were administered two short courses of emtricitabine oral solution (each 3 mg/kg QD x 4 days) during the first 3 months of life. The AUC observed in neonates who received a daily dose of 3 mg/kg of emtricitabine was similar to the AUC observed in pediatric patients ≥3 months to 17 years who received a daily dose of emtricitabine as a 6 mg/kg oral solution up to 240 mg or as a 200 mg capsule (Table 1).

Table 1 Mean ± SD Pharmacokinetic Parameters by Age Groups for Pediatric Patients and Neonates Receiving EMTRIVA Capsules or Oral Solution

	HIV-exposed Neonates	HIV-infected Pediatric Patients			
Age	**0–3 mo (N=20)[1]**	**3–24 mo (N=14)**	**25 mo–6 yr (N=19)**	**7–12yr (N=17)**	**13–17 yr (N=27)**
Formulation Capsule (n) Oral Solution (n)	 0 20	 0 14	 0 19	 10 7	 26 1
Dose (mg/kg)[2]	3.1 (2.9-3.4)	6.1 (5.5–6.8)	6.1 (5.6–6.7)	5.6 (3.1–6.6)	4.4 (1.8–7.0)
Cmax (μg/mL)	1.6 ± 0.6	1.9 ± 0.6	1.9 ± 0.7	2.7 ± 0.8	2.7 ± 0.9
AUC (hr•μg/mL)	11.0 ± 4.2	8.7 ± 3.2	9.0 ± 3.0	12.6 ± 3.5	12.6 ± 5.4
$T_{1/2}$ (hr)	12.1 ± 3.1	8.9 ± 3.2	11.3 ± 6.4	8.2 ± 3.2	8.9 ± 3.3

1. Two pharmacokinetic evaluations were conducted in 20 neonates over the first 3 months of life. Median (range) age of infant on day of pharmacokinetic evaluation was 26 (5–81) days.
2. Mean (range)

Renal Impairment

The pharmacokinetics of emtricitabine are altered in patients with renal impairment **(see PRECAUTIONS)**. In adult patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} and AUC of emtricitabine were increased due to a reduction in renal clearance (Table 2). It is recommended that the dosing interval for EMTRIVA be modified in adult patients with creatinine clearance <50 mL/min or in adult patients with ESRD who require dialysis **(see DOSAGE AND ADMINISTRATION).** The effects of renal impairment on emtricitabine pharmacokinetics in pediatric patients are not known.

Table 2 Mean ± SD Pharmacokinetic Parameters in Adult Patients with Varying Degrees of Renal Function

Creatinine Clearance (mL/min)	**>80 (N=6)**	**50–80 (N=6)**	**30–49 (N=6)**	**<30 (N=5)**	**ESRD[1] <30 (N=5)**
Baseline creatinine clearance (mL/min)	107 ± 21	59.8 ± 6.5	40.9 ± 5.1	22.9 ± 5.3	8.8 ± 1.4
C_{max} (μg/mL)	2.2 ± 0.6	3.8 ± 0.9	3.2 ± 0.6	2.8 ± 0.7	2.8 ± 0.5
AUC (hr•μg/mL)	11.8 ± 2.9	19.9 ± 1.2	25.1 ± 5.7	33.7± 2.1	53.2 ± 9.9
CL/F (mL/min)	302 ± 94	168 ± 10	138 ± 28	99 ± 6	64 ± 12
CLr (mL/min)	213 ± 89	121 ± 39	69 ± 32	30 ± 11	NA[2]

1. ESRD patients requiring dialysis
2. NA = Not Applicable

Hemodialysis: Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Drug Interactions:

At concentrations up to 14-fold higher than those observed in vivo, emtricitabine did not inhibit in vitro drug metabolism mediated by any of the following human CYP 450 isoforms: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation (uridine-5'-disphosphoglucuronyl transferase). Based on the results of these in vitro experiments and the known elimination pathways of emtricitabine, the potential for CYP450 mediated interactions involving emtricitabine with other medicinal products is low.

EMTRIVA has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (DF), zidovudine, indinavir, famciclovir, and stavudine. Tables 3 and 4 summarize the pharmacokinetic effects of coadministered drug on emtricitabine pharmacokinetics and effects of emtricitabine on the pharmacokinetics of coadministered drug.

Table 3 Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug[1]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable

Table 4 Drug Interactions: Change in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine[1]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[2] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↑ 17 (↑ 0 to ↑ 38)	↑ 13 (↑ 5 to↑ 20)	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable

INDICATION AND USAGE

EMTRIVA is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection.

Additional important information regarding the use of EMTRIVA for the treatment of HIV-1 Infection:

- EMTRIVA should not be coadministered with ATRIPLA™, TRUVADA®, or Lamivudine-containing products **(see WARNINGS)**.
- In treatment-experienced patients, the use of EMTRIVA should be guided by laboratory testing and treatment history **(see MICROBIOLOGY)**.

Description of Clinical Studies:

Treatment-Naive Adult Patients

Study 934: EMTRIVA + VIREAD + Efavirenz Compared with Zidovudine/Lamivudine + Efavirenz

Data through 48 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter study comparing EMTRIVA + VIREAD administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve patients. Patients had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4 cell count was 245 cells/mm^3 (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 $\log_{10}$ copies/mL (range 3.56–6.54). Patients were stratified by baseline CD4 count (< or ≥200 cells/mm^3); 41% had CD4 cell counts (<200 cells/mm^3 and 51% of patients had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 5.

Table 5 Outcomes of Randomized Treatment at Week 48 (Study 934)

Outcome at Week 48	EMTRIVA + TDF + EFV (N=244)	AZT/3TC + EFV (N=243)
	%	%
Responder[1]	84%	73%
Virologic failure[2]	2%	4%
Rebound	1%	3%
Never Suppressed	0%	0%
Change in Antiretroviral Regimen	1%	1%
Death	<1%	1%
Discontinued Due to Adverse event	4%	9%
Discontinued for Other Reasons[3]	10%	14%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
3. Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

The difference in the proportion of patients who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label study. In addition, 80% and 70% of patients in the EMTRIVA + VIREAD group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4 cell count was 190 cells/mm^3 in the EMTRIVA + VIREAD group and 158 cells/mm^3 in the zidovudine/lamivudine group.

Through 48 weeks, 7 patients in the EMTRIVA + VIREAD group and 5 patients in the zidovudine/lamivudine group experienced a new CDC Class C event.

Study 301A: EMTRIVA QD + Didanosine QD + Efavirenz QD Compared to Stavudine BID + Didanosine QD + Efavirenz QD

Study 301A was a 48 week double-blind, active-controlled multicenter study comparing EMTRIVA (200 mg QD) administered in combination with didanosine and efavirenz versus stavudine, didanosine and efavirenz in 571 antiretroviral naive adult patients. Patients had a mean age of 36 years (range 18–69), 85% were male, 52% Caucasian, 16% African-American and 26% Hispanic. Patients had a mean baseline CD4 cell count of 318 cells/mm^3 (range 5–1317) and a median baseline plasma HIV RNA of 4.9 $\log_{10}$ copies/mL (range 2.6–7.0). Thirty-eight percent of patients had baseline viral loads >100,000 copies/mL and 31% had CD4 cell counts <200 cells/mL. Treatment outcomes are presented in Table 6 below.

Table 6 Outcomes of Randomized Treatment at Week 48 (Study 301A)

Outcome at Week 48	EMTRIVA + Didanosine + Efavirenz (N=286)	Stavudine + Didanosine + Efavirenz (N=285)
Responder[1]	81% (78%)	68% (59%)
Virologic Failure[2]	3%	11%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	7%	13%
Study Discontinuation for Other Reasons[3]	9%	8%

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48.
2. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 168 cells/mm^3 for the EMTRIVA arm and 134 cells/mm^3 for the stavudine arm.

Through 48 weeks in the EMTRIVA group, 5 patients (1.7%) experienced a new CDC Class C event, compared to 7 patients (2.5%) in the stavudine group.

Treatment-Experienced Adult Patients

Study 303: EMTRIVA QD + Stable Background Therapy (SBT) Compared to Lamivudine BID + SBT

Study 303 was a 48 week, open-label, active-controlled multicenter study comparing EMTRIVA (200 mg QD) to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 adult patients who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV-1 RNA ≤400 copies/mL.

Patients were randomized 1:2 to continue therapy with lamivudine (150 mg BID) or to switch to EMTRIVA (200 mg QD). All patients were maintained on their stable background regimen. Patients had a mean age of 42 years (range 22–80), 86% were male, 64% Caucasian, 21% African-American and 13% Hispanic. Patients had a mean baseline CD4 cell count of 527 cells/mm^3 (range 37–1909), and a median baseline plasma HIV RNA of 1.7 $\log_{10}$ copies/mL (range 1.7–4.0).

The median duration of prior antiretroviral therapy was 27.6 months. Treatment outcomes are presented in Table 7 below.

Table 7 Outcomes of Randomized Treatment at Week 48 (Study 303)

Outcome at Week 48	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)
Responder[1]	77% (67%)	82% (72%)
Virologic Failure[2]	7%	8%
Death	0%	<1%
Study Discontinuation Due to Adverse Event	4%	0%
Study Discontinuation for Other Reasons[3]	12%	10%

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48.
2. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
3. Includes lost to follow-up, patient withdrawal, non-compliance, protocol violation and other reasons.

The mean increase from baseline in CD4 cell count was 29 cells/mm^3 for the EMTRIVA arm and 61 cells/mm^3 for the lamivudine arm.

Through 48 weeks, in the EMTRIVA group 2 patients (0.7%) experienced a new CDC Class C event, compared to 2 patients (1.4%) in the lamivudine group.

CONTRAINDICATIONS

EMTRIVA is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the products.

WARNINGS

Lactic Acidosis/Severe Hepatomegaly with Steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination, including emtricitabine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with EMTRIVA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients Co-infected with HIV and Hepatitis B Virus:

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. EMTRIVA is not indicated for the treatment of chronic HBV infection and the safety and efficacy of EMTRIVA have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of EMTRIVA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue EMTRIVA and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Other:

EMTRIVA is a component of TRUVADA (a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate) and ATRIPLA (a fixed-dose combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate). EMTRIVA should not be coadministered with TRUVADA or ATRIPLA. Due to similarities between emtricitabine and lamivudine, EMTRIVA should not be coadministered with other drugs containing lamivudine, including Combivir, Epivir, Epivir-HBV, Epzicom, or Trizivir.

PRECAUTIONS

Patients with Impaired Renal Function:

Emtricitabine is principally eliminated by the kidney. Reduction of the dosage of EMTRIVA is recommended for patients with impaired renal function **(see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).**

Drug Interactions:

The potential for drug interactions with EMTRIVA has been studied in combination with zidovudine, indinavir, stavudine, famciclovir, and tenofovir disoproxil fumarate. There were no clinically significant drug interactions for any of these drugs **(see CLINICAL PHARMACOLOGY, Drug Interactions)**.

Fat Redistribution:

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy.

The mechanism and long-term consequences of these events are unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including EMTRIVA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Information for Patients:

EMTRIVA is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using EMTRIVA.

Patients should be advised that:

- the use of EMTRIVA has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.
- the long term effects of EMTRIVA are unknown.

- EMTRIVA Capsules are for oral ingestion only.
- it is important to take EMTRIVA with combination therapy on a regular dosing schedule to avoid missing doses.
- redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis:

In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

Mutagenesis:

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Impairment of Fertility:

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Pregnancy:

Pregnancy Category B

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, EMTRIVA should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry:

To monitor fetal outcomes of pregnant women exposed to emtricitabine, an antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1–800–258–4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV:

It is not known whether emtricitabine is secreted into human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in

nursing infants, **mothers should be instructed not to breast-feed if they are receiving EMTRIVA.**

Pediatric Use:

The safety and efficacy of emtricitabine in patients between 3 months and 21 years of age is supported by data from three open-label, non-randomized clinical studies in which emtricitabine was administered to 169 HIV-1 infected treatment-naive and experienced (defined as virologically suppressed on a lamivudine containing regimen for which emtricitabine was substituted for lamivudine). Patients received once-daily EMTRIVA Oral Solution (6 mg/kg to a maximum of 240 mg/day) or EMTRIVA Capsules (a single 200 mg capsule once daily) in combination with at least two other antiretroviral agents.

Patients had a mean age of 7.9 years (range 0.3–21), 49% were male, 15% Caucasian, 61% Black and 24% Hispanic. Patients had a median baseline HIV RNA of 4.6 $\log_{10}$ copies/mL (range 1.7–6.4) and a mean baseline CD4 cell count of 745 cells/mm^3 (range 2–2650). Through 48 weeks of therapy, the overall proportion of patients who achieved and sustained an HIV RNA <400 copies/mL was 86%, and <50 copies/mL was 73%. The mean increase from baseline in CD4 cell count was 232 cells/mm^3 (-945, +1512). The adverse event profile observed during these clinical trials was similar to that of adult patients, with the exception of a higher frequency of hyperpigmentation **(see ADVERSE REACTIONS).**

The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV-positive mothers. Each mother received prenatal and intrapartum combination antiretroviral therapy. Neonates received up to 6 weeks of zidovudine prophylactically after birth. The neonates were administered two short courses of emtricitabine oral solution (each 3 mg/kg QD x 4 days) during the first 3 months of life. Emtricitabine exposures in neonates were similar to the exposures achieved in patients >3 months to 17 years **(see CLINICAL PHARMACOLOGY: Pediatrics).** During the two short dosing periods on emtricitabine there were no safety issues identified in the treated neonates. All neonates were HIV-1 negative at the end of the study; the efficacy of emtricitabine in preventing or treating HIV could not be determined.

Geriatric Use:

Clinical studies of EMTRIVA did not contain sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy **(see PRECAUTIONS, Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).**

ADVERSE REACTIONS

Adult Patients:

More than 2000 adult patients with HIV infection have been treated with EMTRIVA alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase I–III clinical trials.

Studies 301A and 303 - Treatment Emergent Adverse Events: The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical studies 301A and 303 were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the EMTRIVA treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

A summary of EMTRIVA treatment emergent clinical adverse events in studies 301A and 303 is provided in Table 8.

Table 8 Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in ≥3% of EMTRIVA-Treated Patients in Either Study 301A or 303 (0–48 Weeks)

Adverse Event	303		301A	
	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)	EMTRIVA + didanosine + efavirenz (N=286)	Stavudine + didanosine + efavirenz (N=285)
Body as a Whole				
Abdominal pain	8%	11%	14%	17%
Asthenia	16%	10%	12%	17%
Headache	13%	6%	22%	25%
Digestive System				
Diarrhea	23%	18%	23%	32%
Dyspepsia	4%	5%	8%	12%
Nausea	18%	12%	13%	23%
Vomiting	9%	7%	9%	12%
Musculoskeletal				
Arthralgia	3%	4%	5%	6%
Myalgia	4%	4%	6%	3%
Nervous System				
Abnormal dreams	2%	<1%	11%	19%
Depressive disorders	6%	10%	9%	13%
Dizziness	4%	5%	25%	26%
Insomnia	7%	3%	16%	21%
Neuropathy/peripheral neuritis	4%	3%	4%	13%
Paresthesia	5%	7%	6%	12%
Respiratory				
Increased cough	14%	11%	14%	8%
Rhinitis	18%	12%	12%	10%
Skin				
Rash event[1]	17%	14%	30%	33%

1. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction.

Studies 301A and 303 - Laboratory Abnormalities:

Laboratory abnormalities in these studies occurred with similar frequency in the EMTRIVA and comparator groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 9 below.

Table 9 Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in ≥1% of EMTRIVA-Treated Patients in Either Study 301A or 303

Number of Patients Treated	303		301A	
	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)	EMTRIVA + Didanosine + Efavirenz (N=286)	Stavudine + Didanosine + Efavirenz (N=285)
Percentage with grade 3 or grade 4 laboratory abnormality	31%	28%	34%	38%
ALT (>5.0 x ULN[1])	2%	1%	5%	6%
AST (>5.0 x ULN)	3%	<1%	6%	9%
Bilirubin (>2.5 x ULN)	1%	2%	<1%	<1%
Creatine kinase (>4.0 x ULN)	11%	14%	12%	11%
Neutrophils (<750 mm^3)	5%	3%	5%	7%
Pancreatic amylase (>2.0 x ULN)	2%	2%	<1%	1%
Serum amylase (>2.0 x ULN)	2%	2%	5%	10%
Serum glucose <40 or >250 mg/dL)	3%	3%	2%	3%
Serum lipase (>2.0 x ULN)	<1%	<1%	1%	2%
Triglycerides (>750 mg/dL)	10%	8%	9%	6%

1. ULN = Upper limit of normal

Study 934 - Treatment Emergent Adverse Events: A summary of the treatment-emergent adverse events observed in this study are shown in Table 10.

Table 10 **Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 934 (0–48 Weeks)**

	EMTRIVA + TDF + EFV N=257	AZT/3TC + EFV N=254
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Study 934 - Laboratory Abnormalities: Significant laboratory abnormalities observed in this study are shown in Table 11.

Table 11 Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group in Study 934 (0–48 Weeks)

	EMTRIVA + TDF + EFV N=257	AZT/3TC + EFV N=254
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175 U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	2%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%
Hemoglobin (<8.0 mg/dL)	0%	3%
Hyperglycemia (>250 mg/dL)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophils (<750/mm^3)	3%	4%
Fasting Triglycerides (>750 mg/dL)	4%	2%

Pediatric Patients:

Assessment of adverse reactions is based on data from 169 HIV-infected pediatric patients who received emtricitabine through Week 48. The adverse event profile in pediatric patients was generally comparable to that observed in clinical studies of EMTRIVA in adult patients.

Selected treatment-emergent adverse events, regardless of causality, reported in patients during 48 weeks of treatment were the following: infection (44%), hyperpigmentation (32%), increased cough (28%), vomiting (23%), otitis media (23%), rash (21%), rhinitis (20%), diarrhea (20%), fever (18%), pneumonia (15%), gastroenteritis (11%), abdominal pain (10%), and anemia (7%). Treatment-emergent grade 3/4 laboratory abnormalities were experienced by 9% of pediatric patients, including amylase >2.0 x ULN (n=4), neutrophils <750/mm^3 (n=3), ALT >5 x ULN (n=2), elevated CPK (>4 x ULN) (n=2) and one patient each with elevated bilirubin (>3.0 x ULN), elevated GGT (>10 x ULN), elevated lipase (>2.5 x ULN), decreased hemoglobin (<7 g/dL), and decreased glucose (<40 mg/dL).

OVERDOSAGE

There is no known antidote for EMTRIVA. Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients.

No severe adverse reactions were reported.

The effects of higher doses are not known. If overdose occurs the patient should be monitored for signs of toxicity, and standard supportive treatment applied as necessary.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

EMTRIVA may be taken without regard to food.

Adult Patients (18 years of age and older):

- **EMTRIVA Capsules:** one 200 mg capsule administered once daily orally.
- **EMTRIVA Oral Solution:** 240 mg (24 mL) administered once daily orally.

Pediatric Patients (0–3 months of age)

- **EMTRIVA Oral Solution:** 3 mg/kg administered once daily orally.

Pediatric Patients (3 months through 17 years):

- **EMTRIVA Oral Solution:** 6 mg/kg up to a maximum of 240 mg (24 mL) administered once daily orally.
- **EMTRIVA Capsules:** for children weighing more than 33 kg who can swallow an intact capsule, one 200 mg capsule administered once daily orally.

Dose Adjustment in Adult Patients with Renal Impairment:

Significantly increased drug exposures were seen when EMTRIVA was administered to patients with renal impairment, (**see CLINICAL PHARMACOLOGY, Special Populations).** Therefore, the dosing interval of EMTRIVA should be adjusted in patients with baseline creatinine clearance <50 mL/min using the following guidelines (see Table 12). The safety and effectiveness of these dose adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 12 Dose Adjustment in Adult Patients with Renal Impairment

Formulation	Creatinine Clearance (mL/min)			
	≥50 mL/min	**30–49 mL/min**	**15–29 mL/min**	**<15 mL/min or on hemodialysis***
Capsule (200 mg)	200 mg every 24 hours	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours
Oral Solution (10 mg/mL)	240 mg every 24 hours (24 mL)	120 mg every 24 hours (12 mL)	80 mg every 24 hours (8 mL)	60 mg every 24 hours (6 mL)

* Hemodialysis Patients: If dosing on day of dialysis, give dose after dialysis.

Although there are insufficient data to recommend a specific dose adjustment of EMTRIVA in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval similar to adjustments for adults should be considered.

HOW SUPPLIED

EMTRIVA is available as capsules and oral solution.

EMTRIVA Capsules, 200 mg, are size 1 hard gelatin capsules with a blue cap and white body, printed with “200 mg” in black on the cap and “GILEAD” and the corporate logo in black on the body.

They are packaged in bottles of 30 capsules (NDC 61958–0601–1) with induction sealed child-resistant closures.

Store at 25 °C (77 °F); excursions permitted to 15 °C–30 °C (59 °F–86 °F)

EMTRIVA Oral Solution is a clear, orange to dark orange liquid.

EMTRIVA Oral Solution is supplied in plastic, amber bottles of 170 mL (NDC 61958–0602–1) with child resistant closures, packaged with a marked dosing cup.

Store refrigerated, 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).

℞ Only

EMTRIVA is manufactured for Gilead Sciences, Inc., Foster City, CA 94404

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