NDA 21-896 EMTRIVA® (emtricitabine) Oral Solution 10mg/mL LABELING CHANGES

(Changes are highlighted in yellow.)

CLINICAL PHARMACOLOGY

Pediatrics (section and table added)

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.

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

Age	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 14	 0 19	 10 7	 26 1
Dose (mg/kg)[1]	6.1 (5.5–6.8)	6.1 (5.6–6.7)	5.6 (3.1–6.6)	4.4 (1.8–7.0)
C_{max} (μg/mL)	1.9 ± 0.6	1.9 ± 0.7	2.7 ± 0.8	2.7 ± 0.9
AUC (hr•μg/mL)	8.7 ± 3.2	9.0 ± 3.0	12.6 ± 3.5	12.6 ± 5.4
$T_{1/2}$ (hr)	8.9 ± 3.2	11.3 ± 6.4	8.2 ± 3.2	8.9 ± 3.3

[1]mean (range)

Renal Impairment (new language added)

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.

Drug Interactions

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 once 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 once 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 ~~in adults~~ **in patients over three months of age.**

PRECAUTIONS

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)**.

Immune Reconstitution Syndrome (**new section added**)

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis (**new language added**)

~~Long-term carcinogenicity studies of emtricitabine in rats and mice are in progress.~~ 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).

Pediatric Use (**new section added**)

Safety and effectiveness in pediatric patients below the age of 3 months have not been established.

The safety and efficacy of emtricitabine is supported by data from three open-label, non-randomized clinical studies in which emtricitabine was administered to 169 HIV-1 infected treatment naïve and experienced (defined as virologically suppressed on a lamivudine containing regimen for which emtricitabine was substituted for lamivudine) patients between 3 months and 21 years of age. 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).**

ADVERSE REACTIONS

Pediatric Patients (new section added)

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).

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 (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:
(new table added)

Table 9 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).