



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

DATE: September 14, 2006

TO: NDA 21-896 (Emtriva® Oral Solution)

FROM: Jennifer L. DiGiacinto, Pharm.D.
Senior Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4 (DCP4)
Office of Clinical Pharmacology (OCP)

THROUGH: Kellie S. Reynolds, Pharm.D.
Team Leader, DCP4

RE: Clinical Pharmacology Review of Pediatric Data (SE-5)

1. Executive Summary

Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor (NRTI) that is currently approved for the treatment of HIV infection as the following formulations:

- A 200-mg capsule formulation, marketed as EMTRIVA® Capsule.
- A liquid formulation for pediatrics and adults, marketed as EMTRIVA® Oral Solution (10 mg/mL).
- A fixed dose combination with tenofovir disoproxil fumarate (TDF), marketed as TRUVADA®.
- A fixed dose combination with efavirenz (EFV) and TDF, marketed as ATRIPLA®.

The current dosing recommendations for EMTRIVA® and FTC containing products are as follows:

- **EMTRIVA® Capsule:** 200 mg QD for adults > 18 years of age and children weighing > 33 kg.
- **EMTRIVA® Oral Solution:** 240 mg QD for adults \geq 18 years of age and 6 mg/kg QD for children 3 months to < 18 years of age, up to a maximum of 240 mg QD.
- **TRUVADA® and ATRIPLA®:** One tablet QD for adults \geq 18 years of age.

On March 28, 2006, the applicant submitted the remaining data needed to fulfill the Written Request, which is a multiple-dose pharmacokinetic (PK) and safety study in HIV-exposed neonates (FTC-116). On 25May2006, the FDA Pediatric Exclusivity Board determined the applicant had met all the requirements of the FTC Pediatric Written Request and granted pediatric exclusivity for FTC.

In support of this NDA, the applicant adequately addressed the following issues:

- Determined the steady-state FTC concentrations in HIV (exposed) neonates (from birth to 3 months of age).
- Identified that a 3 mg/kg daily dose in neonates (0 to 3 months of age) achieves plasma concentrations in neonates similar to those in pediatric patients (> 3 months to < 18 years of age) and adults when administered at the recommended doses of FTC.

1.1 Recommendation

The clinical pharmacology information submitted to NDA 21-896 (b) (4) is acceptable.

1.2 Post Marketing Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

This NDA Supplement contains one PK and safety study (FTC-116) conducted in neonates (0 to 3 months of age). FTC-116 was conducted to evaluate the PK of FTC in neonates over the first 3 months of life following multiple-dose administration and to assess the effects that changing renal function has on the PK of FTC. Secondary endpoints of FTC-116 were to assess the safety and tolerability of multiple doses of FTC when administered to neonates.

FTC-116 was conducted to evaluate FTC PK and safety following a short course of multiple doses of FTC to establish a dosage regimen for neonates (< 3 months of age). Twenty-one neonates completed the study and were followed for 24 weeks. In summary, FTC-116 established that FTC oral solution dosed at a 3 mg/kg QD produced AUC_{tau} and C_{max} concentrations similar to those shown to be safe and effective in HIV-infected adults and children ≥ 3 months. See the summary data for FTC PK parameters in Table 1 below.

(Table 1) Summary of FTC PK Parameters by Age Group from Study FTC-116

| Parameter | Age Group (Days) (N) | | | |
|-------------------------------|--------------------------|---------------------------|---------------------------|-----------------------------|
| | Group 1 (1-21) (N=18) | Group 2 (22-42) (N=10) | Group 3 (43-90) (N=12) | All Groups (0-90) (n=40) |
| Age (days) | 14 | 34 | 49 | 26 |
| Median (range) | (5-21) | (23-42) | (43-81) | (6-81) |
| Weight (kg) | 3.0 | 3.6 | 4.2 | 3.6 |
| Mean (%CV) | (12) | (18) | (15) | (21) |
| C _{max} (µg/mL) | 1.601 | 1.415 | 1.639 | 1.566 |
| Mean (%CV) | (28) | (23) | (52) | (36) |
| C _{min} (µg/mL) | 0.126 | 0.065 | 0.091 | 0.100 |
| Mean (%CV) | (41) | (42) | (89) | (62) |
| T _{max} (hr) | 2.21 | 2.06 | 1.96 | 2.02 |
| Median (min, max) | (1.92 - 4.17) | (1.92 - 4.000) | (1.03 - 3.83) | (1.03 - 4.17) |
| AUC _{tau} (hr·µg/mL) | 13.44 | 8.55 | 9.27 | 10.96 |
| Mean (%CV) | (28) | (15) | (48) | (38) |
| t _{1/2} (hr) | 12.2 | 12.4 | 12.1 | 12.4 |
| Median (min, max) | (8.9 - 22.2) | (4.0 - 17.9) | (6.7 - 16.7) | (4.0 - 22.2) |
| CL/F (mL/min) | 12.7 | 22.1 | 29.2 | 20.0 |
| Mean (%CV) | (31) | (19) | (64) | (63) |
| CL/F (mL/min/m ²) | 61.4 | 97.7 | 115.0 | 89.4 |
| Mean (%CV) | (34) | (14) | (57) | (51) |

N= Number of PK Assessments in Age Group

Source: Section 11.1, Table 9 in Study Report for FTC-116

Table 2 summarizes the PK data from previous FTC clinical studies conducted in pediatric subjects > 3 months to < 18 years of age (FTC-203, FTC-202, and FTC-211) and Table 3 summarizes PK data from previous FTC clinical studies conducted in healthy volunteers and HIV-infected subjects > 18 years of age. (Figure 1 displays the PK data (median and ranges) for all children dosed with FTC in studies FTC-203, FTC-202, FTC-211, and FTC-116 along with adult PK data (neonates 1-90 days old, pediatric subjects > 3 months to < 18 years of age, and adults > 18 years of age.) The mean AUC_{τ} values observed in neonates who received 3 mg/kg in FTC-116 were similar to values observed in children \geq 3 months of age who received the approval doses for those age groups. Thus, the well defined efficacy profile that has been reported in older pediatric subjects and HIV-infected adults while taking FTC as part of their ART can be extrapolated to the neonate population when administered 3 mg/kg of FTC QD.

(Table 2) FTC Phase 2 Studies (FTC-203, FTC-202, and FTC-211): Mean (%CV) Values for FTC PK Parameters at Steady-State by Age Group for Subjects Receiving Capsules and Solution (6-mg/kg, Maximum Capsule Dose 200-mg and Maximum Oral Solution Dose 240-mg)

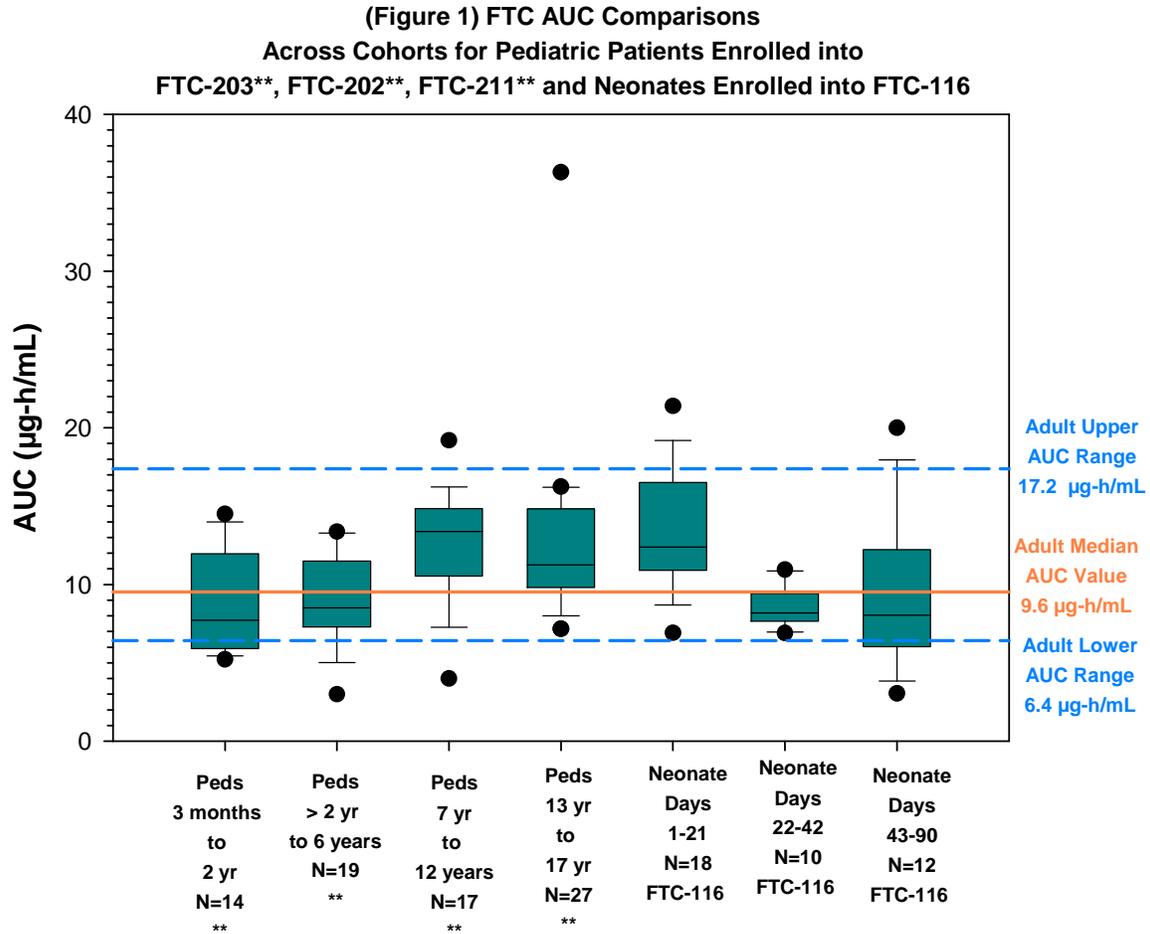
| Age Group | N | | C_{max} ($\mu\text{g/mL}$) | C_{min} ($\mu\text{g/mL}$) | t_{max} (hr) | AUC_{τ} ($\text{hr}\cdot\mu\text{g/mL}$) | $t_{1/2}$ (hr) | CL/F (mL/min/kg) |
|-----------------|-----------------|-------------|-----------------------------------|-----------------------------------|-------------------|--|-------------------|--------------------------------|
| 1 3–24 mo | 14 ^a | Mean CV% | 1.93 34 | 0.059 52 | 1.6 54 | 8.70 37 | 8.87 36 | 13.2 34 |
| 2 25 mo–6 yr | 19 | Mean CV% | 1.91 38 | 0.059 71 | 1.6 62 | 9.03 33 | 11.29 57 | 13.0 46 |
| 3 7–12 yr | 17 | Mean CV% | 2.72 30 | 0.066 45 | 1.7 99 | 12.57 28 | 8.19 39 | 8.4 54 |
| 4 13–17 yr | 27 | Mean CV% | 2.73 31 | 0.064 94 | 1.7 65 | 12.55 43 | 8.94 37 | 6.4 45 |

^a Subject 0104 (Study-FTC-203) was excluded from the summary statistics

Source: Appendix 2.7.2.5, Table 2.7.2.5

(Table 3) Summary of Mean (%CV) Steady-State PK Parameter Estimates in Adults for FTC Following 200-mg Once Daily Dose

| Clinical Study (Protocol) No. | Subjects Number (M/F) Type Age: mean (range) | C_{max} ($\mu\text{g/mL}$) | t_{max} (hr) | C_{min} ($\mu\text{g/mL}$) | AUC_{τ} ($\text{hr}\cdot\mu\text{g/mL}$) | $t_{1/2}$ (hr) | CL/F (mL/min) |
|-------------------------------|---|-----------------------------------|-------------------|-----------------------------------|--|-------------------|-----------------------------|
| FTC-101 | 8 (8M/0F) HIV-infected subjects 37 (29–42) yr | 1.72 (53%) | 2.00 (48%) | 0.05 (24%) | 8.00 (15%) | 8.24 (31%) | 425 (15%) |
| FTC-106 | 5 (5M/0F) Healthy volunteers 37 (33–42) yr | 1.72 (16%) | 1.00 (0%) | 0.07 (28%) | 10.04 (18%) | 10.2 (19%) | 339 (20%) |
| FTC-303 | 12 (1M/11F) HIV-infected subjects 38 (21–61) yr | 1.94 (24%) | 1.80 (58%) | 0.11 (71%) | 11.31 (29%) | 8.08 (32%) | 317 (27%) |

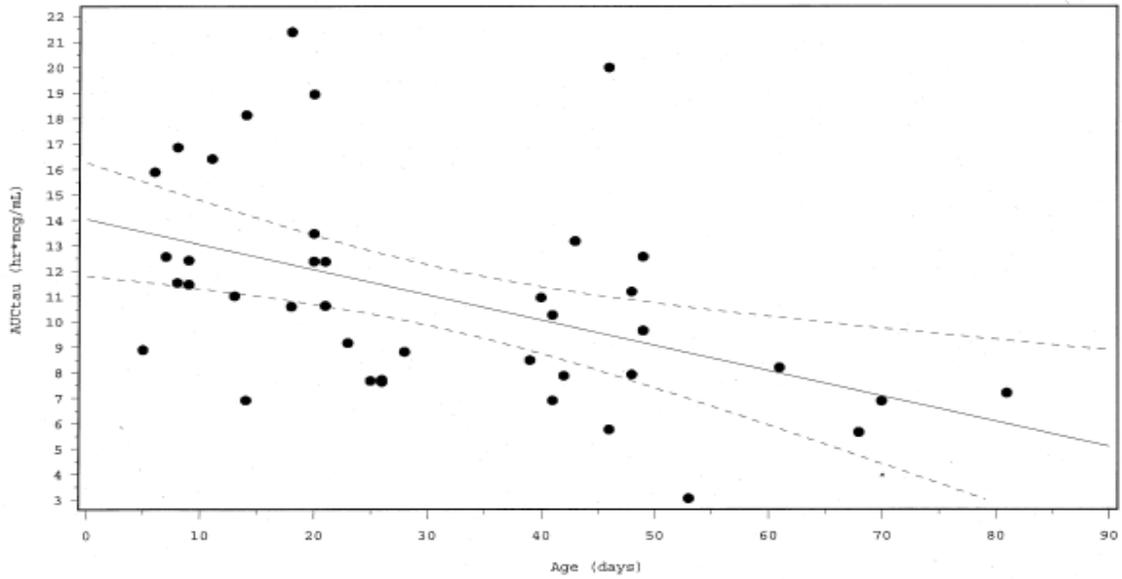


** Data collected in studies FTC-203, FTC-202, and FTC-211

Figure 2 below illustrates a decrease in FTC AUC_{tau} with age that occurred in the neonates (0 -90 days old) enrolled into FTC-116, which corresponds to the increase in FTC CL/F with age depicted in Figure 3 below. The relationships of AUC_{tau} and CL/F with age were examined in a linear regression analysis and are described by the following equations:

- $AUC_{tau} = 14.03 + (-0.099)^{\wedge} \text{Age in days}$ ($r^2 = 0.2230$). The slope of the regression line is statistically different from zero ($p = 0.0004$) with a Spearman correlation coefficient of -0.53.
- $CL/F = 8.19 + 0.383^{\wedge} \text{Age in days}$ ($r^2 = 0.5891$). The slope of the regression line is statistically different from zero ($p < 0.001$) with a Spearman correlation = 0.72.

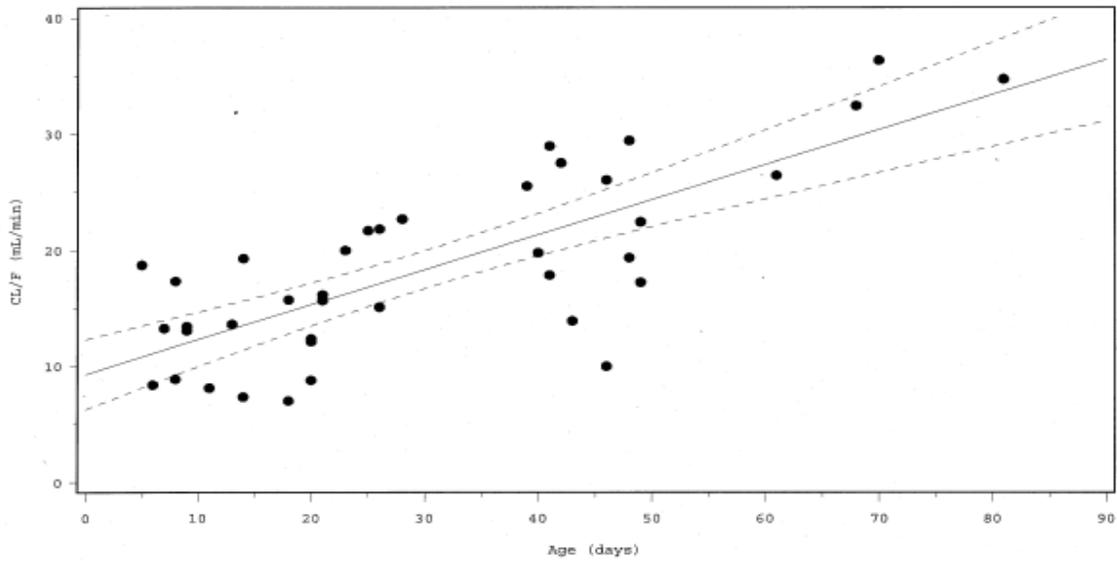
(Figure 2) FTC AUC_{tau} (µg·h/mL) versus Age



AUC_{tau} (hr*mcg/mL) = 14.03 + (-0.099) * Age (days), r² = 0.2230
 Spearman correlation Coefficient= -0.53, p-value<0.001
 Dashed lines represent 95%CI

Source: \\Gilead\FTC\FTC116\programs\graph\graph_pkvsage.sas

(Figure 3) FTC CL/F (mL/min) versus Age



CL/F (mL/min) = 9.31 + 0.301 * Age (days), r² = 0.5891
 Spearman correlation Coefficient= 0.72, p-value<0.001
 Dashed lines represent 95%CI

Source: \\Gilead\FTC\FTC116\programs\graph\graph_pkvsage.sas

Figure 3 indicates the total apparent body clearance (CL/F) increased with age over the first three months of life, which was expected as the neonates renal function matures during this time. The weight range for neonates from birth to 90 days was 2.1 to 5.0 kg (0 – 21 days old weight range = 2.5 -3.8 kg, 22 – 42 days old weight range = 2.1 –

4.3 kg, and 43 – 90 days weight range = 3.1 – 5.0 kg). It is well understood neonates that are carried full-term (36 weeks gestation or later) have immature renal function (glomerular filtration rate (GFR) = 40 mL/min/1.73 m²) compared to adult values (GFR = > 90 mL/min/1.73 m²). It's typically > 8 months postpartum before the infant's renal function approaches GFR values similar to those reported in adults.

In summary:

- FTC-116 established that FTC oral solution dosed at a 3 mg/kg QD produced similar AUC_{tau} and C_{max} concentrations similar to those shown to be safe and effective in HIV-infected adults and children ≥ 3 months.
- The CL/F increased with age over the first three months of life, which was expected as the neonates renal function matures during this time.
- On 25May2006, the FDA Pediatric Exclusivity Board determined the applicant had met all the requirements of the FTC Pediatric Written Request and granted pediatric exclusivity for FTC.

Jennifer L. DiGiacinto, Pharm.D.
Senior Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4, OCP

Concurrence:

Kellie S. Reynolds, Pharm. D
Team Leader, Antiviral Products Section
Division of Clinical Pharmacology 4, OCP

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jennifer DiGiacinto
10/2/2006 10:10:52 AM