



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

DATE: September 19, 2006

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

FROM: Russell Fleischer, PA-C, MPH
Senior Clinical Analyst, DAVP

RE: Medical Review of Pediatric Data (SE-5)

1.0 Background

Emtriva® (emtricitabine, FTC) Tablets and Oral Solution are approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infected patients >3 months of age.

In July 1999, a Written Request was issued under which the applicant, Triangle Pharmaceuticals (now Gilead Sciences), was asked to provide (1) pharmacokinetic, safety and antiviral activity data in pediatric patients with HIV-1 infection, and (2) pharmacokinetic and safety data of emtricitabine in HIV-1 exposed neonates (born to HIV-1 infected mothers). In exchange for this information, an additional 6 months of marketing exclusivity would be granted.

In March 2005, Gilead submitted data supporting use of the oral solution formulation in HIV-1 infected pediatric patients >3 months of age; these data resulted in labeling for this age group. The current submission provides the requested data in the neonatal population.

2.0 Study Review

Study FTC116 was an open-label, non-randomized study conducted in infants born to HIV-1 infected mothers. The objectives were to: evaluate emtricitabine pharmacokinetics over the first three months of life, determine how the maturing renal function of affects pharmacokinetics, and assess safety and tolerability. The trial was conducted at two sites in South Africa under appropriate ethical guidelines.

- **Design**

Pregnant women in their third trimester were screened and if enrolled received, at a minimum, intrapartum intravenous zidovudine (ZDV) at the currently recommended dose. At the Investigator's discretion, as an alternative to the intravenous ZDV, the mother could have been given a single intrapartum dose of nevirapine (NVP) or a short course of oral ZDV. The mother could also have received antepartum and postpartum treatment with an effective antiretroviral regimen using commercially available drugs administered in accordance with the manufacturers' product labels/package inserts. Antepartum treatment was provided during the last trimester of pregnancy, i.e., from gestational Week 28 and later. Postpartum treatment was available for at least 6 months.

Infants born to these HIV-1 infected mothers received six weeks of postnatal ZDV (2 mg/kg every 6 hours) beginning within 6-12 hours of birth. Infants were then assigned to receive two four day courses of emtricitabine 3 mg/kg QD separated by an interval of at least two weeks, as follows:

- Dose Group 1 (n = 4): the first 4-day course of emtricitabine was administered during the 1st week after birth (i.e., Days 1 to 7 postpartum) with the second 4-day course administered during the 3rd to 6th weeks after birth (i.e., Days 15 to 42 postpartum).
- Dose Group 2 (n = 4): the first 4-day course of emtricitabine was administered during the 2nd week after birth (i.e., Days 8 to 14 postpartum) with the second 4-day course administered during the 4th to 7th weeks after birth (i.e., Days 22 to 49 postpartum).
- Dose Group 3 (n = 4): the first 4-day course of emtricitabine was administered during the 3rd week after birth (i.e., Days 15 to 21 postpartum) with the second 4-day course administered during the 5th to 8th weeks after birth (i.e., Days 29 to 56 postpartum).
- Dose Group 4 (n = 4): the first 4-day course of emtricitabine was administered during the 4th week after birth (i.e., Days 22 to 28 postpartum) with the second 4-day course administered during the 6th to 12th weeks after birth (i.e., Days 36 to 84 postpartum).

Serial blood sampling (0 to 48 hours post-dose for full PK evaluation) was performed after administration of the last (4th) dose of each FTC treatment for determination of FTC plasma concentrations.

Infants were followed for a total of 24 weeks postpartum.

- **Study Participants**

Neonates were considered eligible for participation in this study if all of the following criteria were satisfied:

Mothers

The expecting mother must have been in the last trimester of pregnancy, i.e., gestational Week 28 or later with confirmed HIV-1 infection by at least one of the following: HIV-1 culture, HIV-1 DNA PCR, plasma HIV-1 RNA of $\leq 10,000$ copies/mL, neutralizable HIV-1 p24 antigen or licensed HIV-1 ELISA with confirmatory Western Blot. The expecting mother must have given her written informed consent for her child to participate in this study once born, the expecting mother must have been clinically stable, and must have been able and willing to comply with the protocol schedule and procedures, including a possible programmed delivery, if deemed appropriate, and she must have been available to complete the study with her newborn child.

Neonates

The child must have been born to a mother with a confirmed diagnosis of HIV-1 Infection, be at least 36 weeks' gestation at birth and weigh >2.5 kg (>5.5 lbs).

- **Demographic Characteristics of Neonates**

Between June 2004 and May 2005, 29 neonates (including 1 pair of twins) were born to 28 HIV-1 seropositive women. Of these, 22 were enrolled and 21 received at least three doses of emtricitabine.

All 22 neonates were Black, 64% were male, median day 1 height was 48 cm (39.0, 53.0), median day weight was 2.8 kg (2.0, 3.8), median CD4 cell count was 1148 cells/mm³ (838, 2664), and HIV DNA PCR was negative in 19 (0 positive and 3 not done). All neonates had HIV RNA <400 copies/mL at their day 1 (birth) visit.

- **Disposition**

Twenty-two neonates were enrolled, and two discontinued the study: one due to Grade 3 necrotizing enterocolitis with anemia and one did not return to the clinic for the Day 4 visit of the first course of emtricitabine treatment and was lost to follow-up.

- **Assessment of Efficacy**

No infant was HIV positive at the end of the study. CD4 cell counts tended to increase in all patients during the study period.

- **Safety Review**

Neonatal safety was evaluated by the collection of AE reports, physical examination findings, body length and weight, vital signs measurements and clinical laboratory data (hematology and serum chemistry) over an approximately 6-month period postpartum.

Deaths

None.

Serious Adverse Events

Three neonates experienced serious adverse events: Grade 3 necrotizing enterocolitis with Grade 3 anemia prior to receiving study drug, Grade 3 gastroenteritis and bronchopneumonia starting day 106, resolved, and Grade 4 bronchiolitis day 43, resolved.

Discontinuations due to Adverse Events

One neonate discontinued the study due to an adverse event: Grade 3 necrotizing enterocolitis with Grade 3 anemia and was withdrawn by the investigator 15 days after birth and prior to receiving study drug.

General Adverse Events

Treatment emergent adverse events reported in >3 patients included: upper respiratory tract infection, oral candidiasis, candidiasis, lymphadenopathy, constipation or diarrhea, hypoglycemia and pyrexia. The majority of events were classified as mild and/or moderate in severity and most resolved without therapy.

Grade 3 and 4 events occurred in eight neonates: anemia (n=1), neutropenia (n=2), bronchitis (n=1) and hypoglycemia (n=4).

No skin discoloration was observed during the study.

All neonates experienced Grade 1-2 decreases in their hemoglobin and hematocrit levels during the study period. All neonates were receiving concomitant ZDV; anemia is a common related adverse event.

3.0 Clinical Pharmacology

Prior to conducting study FTC116, Gilead conducted study FTC105 which was a single dose escalation pharmacokinetics study in pediatric patients between 22 months and 17 years of age. The results of this study suggested that a dose of 6 mg/kg/day, to a maximum of 240 mg/day, would provide plasma concentrations comparable to adults receiving the approved dose of 200 mg/day.

Because emtricitabine is principally eliminated via renal excretion as unchanged drug, and very young infants do not achieve adult levels of renal function until around 10 to 20 weeks, the dose selected for study FTC116 was one-half of the currently recommended dose, 3 mg/kg/day.

In study FTC116, pharmacokinetic assessments occurred 0-48 hours post-dose for full-profile pharmacokinetic evaluation following the fourth dose in each emtricitabine treatment period. Samples for assessment of trough emtricitabine levels were to be obtained prior to the second and third doses. Pharmacokinetic parameters are presented in Table 1.

Table 1. Summary of Emtricitabine Pharmacokinetic Parameters by Age Group

Parameter	Age Group (Days)			
	1–21 (N = 18)	22–42 (N = 10)	43–90 (N = 12)	0–90 (N = 40)
Age (days) Median (range)	14 (5–21)	34 (23–42)	49 (43–81)	26 (5–81)
Weight (kg) Mean (%CV)	3.0 (12)	3.6 (18)	4.2 (15)	3.6 (21)
C _{max} (µg/mL) Mean (%CV)	1.601 (28)	1.416 (23)	1.639 (52)	1.566 (36)
C _{min} (µg/mL) Mean (%CV)	0.126 (41)	0.065 (42)	0.091 (89)	0.100 (62)
T _{max} (hr) Median (min, max)	2.21 (1.92–4.17)	2.06 (1.92–4.00)	1.96 (1.03–3.83)	2.02 (1.03–4.17)
AUC _{tau} (hr•µg/mL) Mean (%CV)	13.44 (28)	8.55 (15)	9.27 (48)	10.96 (38)
T _{1/2} (hr) Median (min, max)	12.2 8.9–22.2	12.4 4.0–17.9	12.1 (6.7–16.7)	12.4 (4.0–22.2)
CL/F (mL/min) Mean (%CV)	12.7 (31)	22.1 (19)	29.2 (64)	20.0 (63)
CL/F (mL/min/m ²) Mean (%CV)	61.4 (34)	97.7 (14)	115.0 (57)	89.4 (51)

N = number of PK assessments in Age Group

Source: [Section 11.1, Table 9](#)

In summary, 3 mg/kg/day of emtricitabine in neonates < 3 months old produced plasma exposures (AUC) similar to exposure observed using approved doses for HIV-infected adults and children ≥3 months old.

4.0 Label Review

The applicant's label provided information on the pharmacokinetics in neonates born to HIV-1 infected mothers, but did not provide information on the use of Emtriva Oral Solution in this population. There were no safety concerns identified and efficacy could not be determined because all neonates had received at least 6 weeks of Zidovudine. However the data do support the use of emtricitabine in neonates. There is the additional concern that the inclusion of pharmacokinetic data without use or dosing information will fail to provide proper guidance to clinicians.

Therefore, the **PRECAUTIONS: Pediatrics** section of the label will be revised to include the following text:

In addition, the pharmacokinetic data will be included in the Clinical Pharmacology section. The Dosage and Administration section will be revised to include dosing instructions for emtricitabine oral solution in neonates (3 mg/kg QD).

5.0 Recommended Regulatory Action

The supplement contains sufficient data to support the safety of a 3 mg/kg/day dose of Emtriva® Oral Solution administered to neonates born to HIV-1 infected mothers. The data would not support a claim that emtricitabine effects mother-to-child transmission. The submission also provides the last component of the pharmacokinetic, safety and antiviral activity data of Emtriva Oral Solution and Capsules in the pediatric population, and as such fully responds to the requests made in the Written Request. Therefore, an additional six months of marketing exclusivity will be granted.

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

/s/

Russell Fleischer
12/13/2006 02:01:14 PM