CLINICAL REVIEW

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Reviewer Name	Russell Fleischer, PA-C, MPH with input from Susan Zhou, PhD (Statistical Reviewer)
Review Completion Date	September 23, 2005
Established Name	Emtricitabine
Trade Name	Emtriva® Oral Solution
Therapeutic Class	Anti-HIV-1 Nucleoside Analogue
Applicant	Gilead Sciences, Inc.
Priority Designation	P
Formulation	Oral solution
Dosing Regimen	6 mg/kg/day (max 240 mg/day)
Indication	Treatment of HIV-1 infection
Intended Population	Pediatric patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The safety, pharmacokinetic and antiviral activity reviewed in this NDA support the approval of Emtriva® (emtricitabine, FTC) Oral Solution. Specifically, the Applicant submitted adequate data characterizing the pharmacokinetics of Emtriva Oral Solution in pediatric patients that supports a dose of 6 mg/kg/day (maximum 240 mg/day). Further, the application contained safety, pharmacokinetic and antiviral activity data from 169 HIV-1 infected pediatric patients aged 3 months to 17 years treated with Emtriva® Oral Solution or Emtriva® Capsules in combination with other antiretroviral agents for at least 48 weeks. The data demonstrate comparable exposures (e.g., AUC), safety and efficacy (proportion with HIV RNA <400 c/mL and increases in CD4 cell counts) in pediatric compared to adult patients. Of note, hyperpigmentation manifested as skin discoloration on the palms and soles, occurred substantially more frequently in pediatric patients compared to adults (32% versus 13%); although the etiology remains under investigation, all cases appeared mild with most resolving upon discontinuation of emtricitabine. Finally, the oral solution provides an opportunity for improved dosing in patients with renal impairment; once daily dosing from once every two to four days based on creatinine clearance.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Emtriva Capsules have been marketed in the US since September 2004 with a patient package insert. No post-marketing concerns have emerged. As such, no new risk management activity is required.

1.2.2 Required Phase 4 Commitments

- The Applicant is continuing to assess the mechanism of action and clinical significance of hyperpigmentation.
- To address the requirements of PREA, the Applicant has committed to submit the results of an ongoing study of the pharmacokinetics, safety and antiviral activity of emtricitabine in patients 0 (birth) to 3 months of age; a study report is due in March 2006.

1.2.3 Other Phase 4 Requests

There are no new Phase 4 requests for Emtriva Oral Solution.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Emtriva (emtricitabine) Capsules is a member of the class of anti-HIV-1 nucleoside reverse transcriptase inhibitors used in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients >18 years of age.

The clinical program to support approval of Emtriva Oral Solution and Capsules in patients <18 years of age included three clinical studies in which 169 HIV-1 infected pediatric patients (3 months to 21 years of age) received emtricitabine (122 as oral solution and 47 as capsules) in combination with at least two other antiretroviral agents for at least one year (48 weeks). In addition, data were submitted from three clinical pharmacology studies that assessed bioavailability, food effect, and dose-ranging of emtricitabine administered as the oral solution and capsule.

1.3.2 Efficacy

Overall, 83% of pediatric patients achieved and maintained HIV RNA <400 c/mL through 48 weeks of therapy with 73% achieving HIV RNA <50 c/mL. Across all study participants, the median viral load reduction was -3.25 $\log_{10}$ c/mL, the median increase in CD4 cell counts was +198/mm^3 and there were few progressions to advanced CDC stage of disease. These results compare favorably with the efficacy of emtricitabine-containing regimens in adults. However, since emtricitabine was a component of triple drug regimens, and no comparator arms were utilized in any of the clinical trials, the absolute contribution of emtricitabine to efficacy could not be specifically determined.

There were no significant differences in outcomes based on age, degree of antiretroviral experience, or formulation of emtricitabine (Capsules or Oral Solution) used.

1.3.3 Safety

Emtriva® is an approved product with a well characterized safety profile. There was no data in this NDA to suggest that there is a substantial difference in either the types or frequencies of treatment-related adverse events, with the exception of hyperpigmentation, between adult and pediatric patients.

Based on data from previously reviewed trials in HIV-1 infected adults, the common adverse events related to emtricitabine included: headache, nausea, vomiting, diarrhea, rash, skin discoloration (primarily amongst non-Caucasians), elevated ALT and AST levels and neutropenia. The pattern of adverse events was similar between pediatric and adult patients. Headache and nausea occurred less frequently in pediatric patients, while pediatric patients experienced more vomiting, gastroenteritis, fever and infections than adult patients. The higher frequency of vomiting and gastroenteritis may be attributable to the prevalence of gastrointestinal diseases in developing countries as well as the concomitant administration of protease inhibitors.

Of note, there was a case of angioedema associated with rash; as a result, angioedema will be added to the product label.

Hyperpigmentation was reported in 32% (42/132) of pediatric patients compared to 13% in adults. The pattern of skin discoloration was similar to adults, affecting feet and or hands, rarely

the tongue, nails and lips. All but one case was considered mild severity and all but one affected patient was of black African descent. No patient discontinued study medications due to skin discoloration, and 16 (38%) experienced resolution. The mechanism and clinical significance of skin discoloration remains unknown, and the Emtriva labeling includes this information. The applicant is evaluating the nature of these lesions as part of a post-marketing commitment.

1.3.4 Dosing Regimen and Administration

The dose of 6 mg/kg/day (to a maximum of 240 mg) was based on the results of Phase 1 clinical pharmacology studies. The adult dose of emtricitabine, 200 mg QD, was identified in Phase 1/2 trials as being the dose which produced acceptable antiviral activity when given for 14 days of monotherapy and was used in Phase 3 studies of the capsule formulation. In a Phase 1 single-dose trial (Study FTC-105), pharmacokinetic data demonstrated that emtricitabine exposure, expressed as AUC_{tau}, achieved in children receiving a dose of 6 mg/kg QD up to 200 mg, was comparable to the exposure achieved in adults receiving a dose of 200 mg QD, but the oral solution was approximately 20% less bioavailable compared to the capsule formulation. Taking into account the lower bioavailability of the oral solution, the initial dosing recommendation of a maximum of 200 mg/day was modified to allow the emtricitabine oral solution to be administered to a maximum dose of 240 mg. Pharmacokinetic data from patients in the three clinical trials confirmed that the 6 mg/kg/day (to a maximum of 240 mg/day) achieved the targeted AUCs.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were conducted during development of the capsule formulation of emtricitabine. Relevant drug-drug interaction information, including recommendations for dose adjustments of emtricitabine or other agents, is included in the Emtriva Capsule label; these will also be included in the Emtriva® Oral Solution label.

1.3.6 Special Populations

In addition to pediatric patients, Emtriva Oral Solution could be used by adults who cannot take or tolerate capsules and by patients with renal and/or hepatic insufficiency. Pharmacokinetic data included in this NDA led to calculations that would allow emtricitabine oral solution to be administered to adult patients with renal impairment once daily based on creatinine clearance versus every two to four days for the capsule formulation. There are no data to support dose adjustments for pediatric patients with renal impairment. It would be extremely difficult for a sponsor to identify sufficient pediatric patients with HIV-1 infection and renal impairment to conduct such a study in that population. However, based on the adult data, it is likely that clinicians could use a similar dosing regimen in pediatric patients with renal impairment.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Emtricitabine (FTC) is a cytosine nucleoside reverse transcriptase inhibitor (NRTI) approved for use in combination with other antiretroviral agents for treatment of adults with HIV-1 infection. The current application provides data to support the intended indication of treatment of pediatric patients with HIV-1 infection.

Emtricitabine has a similar chemical structure as lamivudine (3TC) except for a fluoride residue at position 5 on the pyrimidine ring. In cells, emtricitabine is phosphorylated to a 5'-triphosphate (FTC-TP) much the same way as Epivir® (3TC, GlaxoSmithKline) is phosphorylated to its active triphosphate (3TC-TP). Both agents are approved for once daily administration, and FTC and 3TC share a common resistance profile. In comparative clinical studies, Emtriva demonstrated similar efficacy and safety as 3TC (see NDA 21,500 study FTC-303). Therefore, at the time the Emtriva NDA was submitted, the Division determined that Emtriva did not appear to offer any significant advantages over the already marketed Epivir, so the application was granted traditional approval and reviewed on a standard review timeline (10 months).

2.2 Currently Available Treatment for Indications

There are currently 22 individual drugs approved in the US for the treatment of HIV infection.

The nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of compounds to exhibit anti-HIV efficacy. Currently there are 8 NRTI's marketed in the US: zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), emtricitabine (Emtriva™), and tenofovir (Viread®), sometimes also referred to as a nucleotide). Additional classes of antiretroviral agents include the non-nucleoside reverse transcriptase inhibitors (NNRTI), including delavirdine (Rescriptor®), nevirapine (Viramune®), and efavirenz (Sustiva®), protease inhibitors (PI), represented by indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®), fosamprenavir (Lexiva®), atazanavir (Reyataz®), tipranavir (Aptivus®) and lopinavir/ritonavir fixed dose combination (Kaletra®), and a GP41 fusion inhibitor, enfuvirtide (Fuzeon®).

A number of the above listed medications are approved for use in various pediatric populations.

2.3 Presubmission Regulatory Activity

(b) (4)

The 200 mg emtricitabine capsule formulation was approved in the United States on 2 July 2003 for marketing in the United States for the treatment of adult HIV-1 infection (NDA 21-500). Currently, Emtriva Capsules and Oral Solution are approved in the European Union, Israel, Argentina, Mexico, and Australia.

On 16 July 1999, a Pediatric Written Request for emtricitabine (as amended 2 March 2001, 20 October 2002, and 3 December 2004) was issued requesting pharmacokinetic and safety data in pediatric HIV-1 infected patients.

The current application was submitted on March 29, 2005, and provides pharmacokinetic, safety and antiviral activity data that addresses the request for data in pediatric patients >3 months of age. A study evaluating emtricitabine pharmacokinetics in the neonatal period (FTC-116) is ongoing. Data from this study will be submitted to support prescribing information for use of emtricitabine in patients aged 0 (birth) to 3 months. The data from study FTC-116 will address the outstanding terms of the Pediatric Written Request and permit a pediatric exclusivity determination. The information is currently planned for submission in March 2006.

2.4 Other Relevant Background Information

Emtriva Capsules were approved in the United States in July 2003 and are currently approved in several countries around the world. Emtriva Oral Solution is currently approved in the European Union. Neither Emtriva Capsules nor Oral Solution has been taken off the market in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

For a detailed discussion of Chemistry, Manufacturing and Controls, please see Dr. Lunn's review.

Emtriva® Oral Solution will be supplied as a clear, orange to dark orange liquid. The daily recommended dose is 6 mg/kg (to a maximum of 240 mg) administered one time per day. The composition of Emtriva Oral Solution is provided in Table 1.

Table 1. Composition of Emtriva® Oral Solution

Component	Quantity/100 mL
Emtricitabine	(b) (4)
Cotton Candy flavor	
Edetate disodium	
FD&C Yellow #6	
Methylparaben	
Monobasic sodium phosphate	
Propylene Glycol	
Propylparaben	
Purified water	
Sodium hydroxide	
Xylitol	

At the maximum recommended dose of 6 mg/kg/day (240 mg/day maximum), patients would receive approximately (b) (4) of propylene glycol; substantially below The World Health Organization recommended limit of (b) (4)/day (see Section 7.1.9).

The process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the pivotal clinical studies. The regulatory specification for Emtriva Oral Solution includes description, identification, assay, content uniformity, chromatographic impurity/degradation products, polymorphic form, dissolution, and microbial attributes.

Stability data indicate that the drug product is generally stable at 25°C/40% relative humidity (RH) for 24 months and at 30°C/45% (RH) for six months. Twenty-four months of supportive stability data on three lots demonstrated no significant time-dependent degradation, and all stability tests were within predetermined specifications. Therefore, the data submitted support a shelf-life of 24 months.

Emtriva Oral Solution will be packaged in (b) (4) amber (b) (4) bottles with a (b) (4) child-resistant cap. Emtriva Oral Solution should be stored refrigerated at 2-8° C [36-46° F], but may be kept at room temperature for up to 48 hours after opening.

All pre-approval inspections of drug substance and drug product manufacturing and testing sites were determined to be acceptable by the Office of Compliance.

3.2 Animal Pharmacology/Toxicology

All animal pharmacology/toxicology studies were conducted during development of Emtriva Capsules. Recently completed carcinogenicity studies demonstrated that emtricitabine is not oncogenic.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data submitted in this application was derived from two clinical studies conducted by the applicant and one study conducted by the Pediatric AIDS Clinical Trials Group (PACTG) of the NIH with support from the applicant.

4.2 Tables of Clinical Studies

Table 2 presents a schematic overview of the principal pediatric clinical studies submitted to support the safety and efficacy of Emtriva® Oral Solution

Table 2. Pivotal Emtriva® Oral Solution HIV Studies

Protocol No. **Countries**	**Start Date**	**Design** **Population**	**Treatment Regimens**	**No. Patients Treated** **Ages**
FTC-203 US, Mexico, Panama, South Africa	February 7, 2001 Ongoing	Open-label Naïve with no or limited prior ART exposure	ART naïve: FTC+d4T+LPV/r ART experience: FTC+background ART without 3TC	ART naïve: 71 ART exp: 45 Total: 116 3-24 mo: 16 25 mo-6 y : 68 7-12 y: 29 13-17 y: 3
FTC-202 (PACTG 1021) US, Panama, Mexico, South Africa	November 2000 Ongoing	Open-label Naïve	FTC+ddI+EFV	ART naïve: 37 3-12 y : 21 13-21 y: 16
FTC-211 Romania	May 2001 Completed	Open-label Naïve with no or very limited prior ART exposure	FTC+ddI+EFV	ART naïve: 15 ART exp: 1 7-12 yr: 1 13-17 y: 15

4.3 Review Strategy

All three clinical trials were reviewed in their entirety.

4.4 Data Quality and Integrity

DSI inspections of studies FTC-203 and FTC-202 were conducted. For study FTC-203, two sites in the Republic of South Africa

Two US-based investigators contributed patients to studies FTC-203 and FTC-202, Dr. Patricia Flynn of St. Jude's Research Hospital in Memphis, Tennessee, and Dr. Ram Yogev of the University of Chicago. Both sites were inspected by the Division of Scientific Investigations. Dr. Flynn was found to have adhered to all applicable requirements and regulations. At Dr. Yogev's site, insignificant violations that did not impact the overall conduct or outcomes of the studies were found. Dr. Ndiweni from Helen Joseph Hospital and Dr. Volari from the University of the Witwatersrand, both in Johannesburg, South Africa (study FTC-203) were found to have generally complied with all applicable US regulations regarding trial conduct.

4.5 Compliance with Good Clinical Practices

It appears that the three clinical trials were conducted in compliance with Good Clinical Practices and in accordance with acceptable ethical standards.

4.6 Financial Disclosures

Pursuant to 21 CFR 54.2(e) the financial certification statement provided by the applicant was reviewed. The applicant requested that all investigators and sub-investigators from studies GS-62-0101, FTC-110, FTC-105, FTC-203 and FTC-211 to disclose proprietary interest or significant equity as defined in the regulations. The applicant has included a list of all investigators and sub-investigators who responded to their request on form 3454 attesting to the absence of financial interest or arrangement. The applicant was not able to obtain information regarding potential financial interest or arrangements from four investigators for study FTC-203. Study FTC-202 (PACTG 1021) was conducted by the Pediatric AIDS Clinical Trials Group of the NIH; no financial information for investigators was provided.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Bioequivalence, dose ranging in pediatric patients, and the impact of food on pharmacokinetics, were assessed in three clinical pharmacology studies (GS-US-162-0101, FTC-110, and FTC-105). A daily AUC of at least 6hr*µg/mL was targeted (10^{th} percentile of the adult AUC given 200 mg once daily). The 6 mg/kg dose (up to a maximum of 200 mg) administered to pediatric patients produced comparable exposures to adults given a 200 mg dose. Taking into account the ~ 20% lower bioavailability of emtricitabine oral solution, relative to the capsule formulation, the initial dosing recommendation was modified to allow the emtricitabine oral solution to be administered at 6 mg/kg QD up to a maximum dose of 240 mg. Pharmacokinetics was also assessed in the three clinical trials. The overall results of the pharmacokinetic data demonstrate:

Adequate numbers of patients between 3 months and 17 years of age were included to characterize pharmacokinetics.

- The FTC AUC_{tau} achieved in children receiving 6 mg/kg/day (to a maximum of 240 mg/day) was similar to exposures achieved in adults receiving 200 mg.
- Younger children had higher variability in pharmacokinetics compared to adults, which may have been due to higher rates of drug clearance or difficulties in administering the oral formulation to younger children.
- Emtriva Oral Solution can be administered without regard to food intake.

Therefore, based on the approximately 20% lower bioavailability of the solution formulation compared to the capsule formulation, the recommended dosing schedule for pediatric patients is:

- Emtriva Oral Solution 6 mg/kg/day (to a maximum of 240 mg/day).
- Emtriva Capsules 1 x 200 mg capsule once daily for children >33 kg and who can swallow an intact capsule.

5.2 Pharmacodynamics

It is not ethical to administer emtricitabine for more than a couple of days as a monotherapy because of the rapid development of resistance. Emtricitabine was used as a component of triple drug antiretroviral regimens, so it is not possible to determine its contribution to changes in HIV RNA.

5.3 Exposure-Response Relationships

For the reasons described above under 5.2, no Exposure-Response assessments were conducted.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is "Emtriva Oral solution in combination with other antiretroviral agents for the treatment of patients >3 months of age with HIV-1 infection".

6.1.1 Methods

The three clinical studies, FTC-202, FTC-203 and FTC-211, were reviewed in their entirety.

6.1.2 General Discussion of Endpoints

Standard validated endpoints of proportion of patients with HIV RNA <400 and <50 c/mL and increases in CD4 cell counts through 48 weeks of anti-HIV therapy were utilized in the clinical studies. These endpoints have been well validated and are utilized by sponsors, FDA, and clinicians to determine efficacy of anti-HIV drugs.

6.1.3 Study Design

Three open-label non-comparative studies provide the basis for the evaluation of efficacy of emtricitabine in patients 3 months to 18 years of age.

FTC-203 is an ongoing open-label study of a once daily dose of emtricitabine in combination with other antiretroviral agents in (treatment naïve) HIV-infected pediatric patients. The primary study objectives are: to obtain steady-state pharmacokinetics, antiviral activity and long-term safety experience for antiretroviral regimens containing emtricitabine in HIV-1 infected pediatric patients. Enrollment was completed in June 2003 with 117 HIV-infected children enrolled. In Latin America and South Africa the study will proceed until the last patient completes 96 weeks, and then FTC will be made available via rollover protocols. Currently 95 children continue on study: 54 in South Africa, 3 in Mexico, 24 in Panama, and 14 in the United States

The dose of emtricitabine is 6 mg/kg to a maximum of 240 mg or 1-200 mg capsule. Treatment naïve patients receive stavudine (d4T) and lopinavir/ritonavir (LPV/r) in addition to emtricitabine. Patients were allowed to enroll if they had virologic suppression (HIV RNA <400 c/mL) on an antiretroviral regimen containing 3TC; these patients switched from 3TC to FTC and remained on their other background antiretroviral agents.

Study *FTC-202 (PACTG 1021, conducted under IND 62,647 by the Division of AIDS, NIH)* is an ongoing open-label study to evaluate the safety, tolerance, antiviral activity and pharmacokinetics of emtricitabine in combination with efavirenz (EFV) and didanosine (ddI) in a once-daily regimen in HIV-infected antiretroviral therapy naïve or very limited antiretroviral exposed pediatric subjects 3 months to 21 years of age. Patients were stratified into three age groups: 90 days to <3 years, 3-12 years, and 13-21 years; however, no patients <3 years of age were enrolled. The objectives are to: determine the long-term safety and tolerance, antiviral

activity, and steady-state pharmacokinetics of a regimen of emtricitabine (6 mg/kg/day to a maximum of 200 mg) plus ddI+EFV; all three agents being administered once daily.

Thirty-seven patients from 16 clinical sites were enrolled and have completed 48 or more weeks of study. The planned enrollment was amended to 53 patients to allow accrual of 16 children in the youngest age category (90 days to < 3 years) because an efavirenz dosing algorithm has recently become available for this age group. Treatment duration has been formally extended to 192 weeks for children ≥3 years of age and 96 weeks for newly enrolling children less than 3 years old.

FTC-211 was an open-label study of a once-daily dose of emtricitabine in combination with other antiretroviral agents in HIV-infected pediatric patients**.** The objectives were: to obtain safety, antiviral activity and pharmacokinetic data for antiretroviral regimens containing emtricitabine in HIV-1 infected pediatric subjects who were treatment naïve or with limited antiretroviral experience between 3 months and 17 years of age. This study was conducted at two sites in Romania and ended on 21 July 2004. Sixteen patients were enrolled; 1 was between 7-12 years and 15 were between 13-17 years. All patients were placed on a regimen of FTC (6 mg/kg QD to a maximum of 240 mg) + ddI+EFV. In this study, treatment experienced was defined as no previous treatment with an ART regimen(s) that included 3TC and/or an NNRTI and a screening plasma HIV-1 RNA level of ≤600,000 c/mL.

Demographic and disease characteristics for pediatric patients are presented in Table 3. In general, the study populations represented a reasonable cross-section of pediatric patients with HIV-1 infection.

Table 3. Demographic and disease characteristics of pediatric enrollees

Characteristic	FTC-203 (n=116)		FTC-202	FTC-211
	Naïve (n=71)	Exp. (n=45)	(n=37)	(n=16)
Gender				
Male	37 (52%)	18 (40%)	20 (54%)	8 (50%)
Female	34 (48%)	27 (60%)	17 (46%)	8 (50%)
Age (mean)	4.8	7.4	11.6	14
Range	0.3-12	1.1-15.9	3.2-21.1	12.8-15.2
Race				
Caucasian	0	4 (9%)	5 (14%)	16 (100%)
Black	63 (89%)	17 (38%)	23 (62%)	
Hispanic	8 (11%)	24 (53%)	9 (24%)	
Base HIV-RNA (log_{10} c/mL)				
Median	5.02	1.74	4.74	4.88
Range	3.75-5.88	1.70-3.68	3.56-6.37	4.03-5.75
Base CD4+/mm^3				
Median	714	1045	310	372.5
Range	186-1886	360-2650	2-1893	266-1100
CDC Clinical Category (%)				
A	25 (35%)	7 (16%)	22 (60%)	4 (25%)
B	26 (37%)	21 (47%)	7 (19%)	8 (50%)
C	13 (18%)	9 (20%)	5 (14%)	4 (25%)
None			3 (8%)	

Further to the breakdown of age, 16 patients were 3-24 months, 81 were 25 months to 6 years, 38 were 7-12 years, 29 were 13-17 years and 5 were 18-21 years of age.

In studies FTC-203 and FTC-211, 46 patients were classified as being “treatment experienced”. Among the 45 described as treatment experienced in study FTC-203, 21 were receiving a 3TC-based regimen as their first antiretroviral agent and had HIV RNA <400 c/mL at the time they switched 3TC for FTC; 21/46 (46%) were receiving their first antiretroviral regimens at the time of the switch. This likely reflects the reason for the substantially lower baseline HIV RNA and higher CD4 cell counts in the treatment experienced group relative to the other groups of treatment naïve patients. Lamivudine and emtricitabine are structurally similar, produce similar antiviral efficacy, and share a common resistance pathway. The Division has previously considered these two agents to be essentially similar. Since 26 patients were suppressed while receiving 3TC, and were doing well as evidenced by virologic suppression, it is difficult to classify these patients as being treatment experienced.

One patient in study FTC-211 was treatment experienced in that he had experienced virologic failure following approximately 7 years of zidovudine and zalcitabine therapy; at study entry the patient had an HIV RNA level of 281,000 c/mL.

Across the three clinical studies, 47 patients were randomized to receive Emtriva® Capsules and 122 to Emtriva® Oral Solution. The demographic characteristics were similar between formulation groups; patients over 6 years of age or >33 kg received the capsule formulation more often than the oral solution.

In all studies, the initial treatment duration was 48 weeks. Patients in Study FTC-203 with HIV RNA <400 c/mL at week 48 are being allowed to continue to receive emtricitabine until the oral solution is marketed or they met certain virological failure criteria. The treatment duration for patients with virologic suppression in study FTC-202 has been extended to 192 weeks.

Overall, 92% (156/169) completed 48 weeks of therapy. Five patients discontinued due to documented virologic failure, four for adverse events (two rash, one each anemia and pancreatitis), and four withdrew consent (e.g., did not wish to continue).

Emtricitabine has *in* vitro activity against chronic hepatitis B virus (HBV). As such patients co-infected with HIV and HBV were eligible to enroll in the clinical studies. Very few HIV/HBV co-infected patients were enrolled; therefore, no conclusion about the safety or efficacy of emtricitabine in this population could be reached.

6.1.4 Efficacy Findings

Overall efficacy assessed as HIV RNA <400 c/mL (using the Roche Amplicor Monitor® Standard and <50 c/mL using the Ultrasensitive Test) and change in CD4 cell count at week 48 was based on all 169 patients Efficacy was calculated by the applicant using a various analytical approaches to confirm the applicant's findings. Patients who discontinued for any reason prior to week 48 are summarized below (see Section 7.1.3.1).

Although two studies have allowed patients to continue on therapy beyond week 48, week 48 was chosen as the time point for analyses of efficacy as this was the original protocol-defined treatment duration for all three studies. Table 4 shows the results of the applicant's efficacy analyses; the analyses were replicated and the conclusions confirmed by the FDA Statistical Reviewer, Dr. Susan Zhou.

Table 4. Efficacy outcomes through 48 weeks

Efficacy Parameter	FTC-203 (n=116)	FTC-202 (n=37)	FTC-211 (n=16)	Overall (n=169)
Δ HIV-RNA (median) (range)	- 3.22 $\log_{10}$ (-4.18, -0.07)	-3.26 $\log_{10}$ (-3.93, -2.40)	-3.31 $\log_{10}$ (-4.05, -2.30)	-3.26 $\log_{10}$ (-4.18, -0.07)
<400 c/mL	104 (90%)	30 (81%)	11 (69%)	145 (86%)
<50 c/mL	86 (74%)	27 (73%)	10 (63%)	123 (73%)
Virologic failure[1]	12 (10%)	7 (19%)	5 (31%)	24 (14%)
Δ CD4+ (median) (range)	+183/mm^3 (-813,+2036)	+210/mm^3 (-1032, +968)	+201/mm^3 (-107, +366)	+232/mm^3 (-1032, +2036)

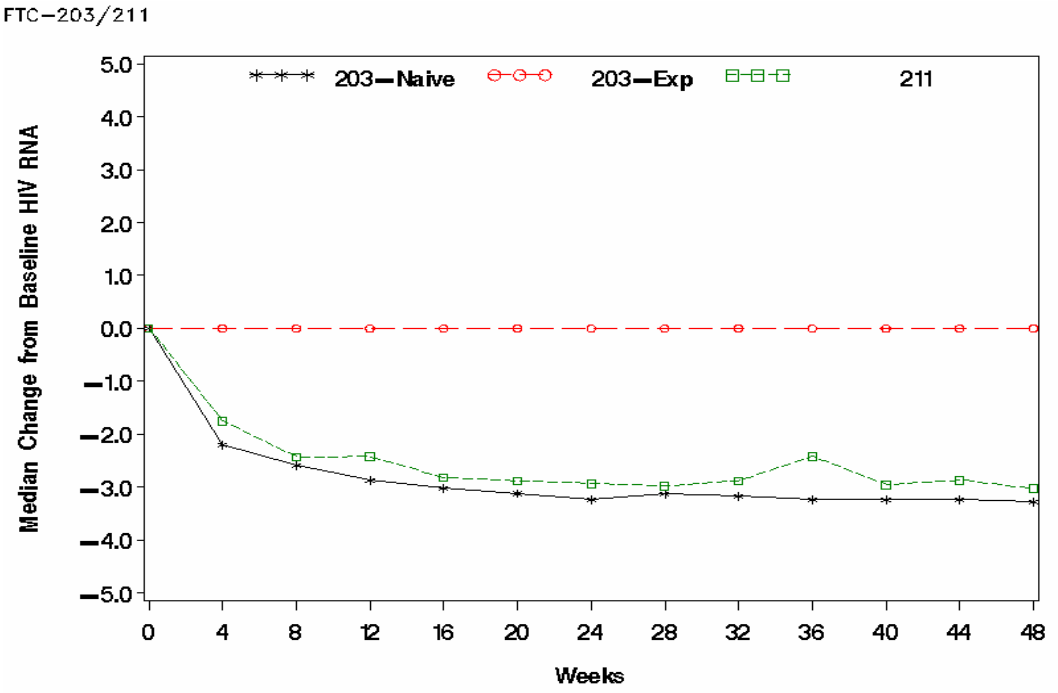
1: Defined as failure to achieve virologic suppression ((400 c/mL) or rebound after virologic suppression (2 values above LLOQ after achieving <400 c/mL), or prematurely discontinued the study.

Ninety-three percent of treatment naïve and 84% of treatment experienced patients in study FTC-203 achieved HIV RNA <400 c/mL. It also appears that treatment experienced patients maintained their baseline viral load levels while treatment naïve patients experienced a median 2.0 $\log_{10}$ c/mL reduction from baseline at Week 4, a 3.0 $\log_{10}$ c/mL reduction after Week 16, and maintained their viral load levels through Week 48. Virologic failure occurred in three naïve and five experienced patients. The one treatment experienced patient in Study FTC-211 was treated successfully and achieved HIV RNA <400 c/mL and <50 c/mL sustained to week 48.
The median reduction from baseline in viral load for patients in FTC-211 was similar to the reduction observed in study FTC-203: -2-3 $\log_{10}$ c/mL.

Patients who received emtricitabine with Kaletra, a protease inhibitor, in study FTC-203 had somewhat higher response and lower virologic failure rates than patients in studies FTC-202 and FTC-211 who received the NNRTI Efavirenz. The explanation for this finding may be related to the higher virologic failure rates among the NNRTI recipients; however, no resistance assessments were conducted. The differences are not substantial enough to warrant a specific recommendation that emtricitabine be administered only with protease inhibitors.

Figure 1 presents the change from baseline in HIV RNA among treatment naïve and experienced patients in study FTC-203 and all patients in study FTC-211.

Figure 1.



The overall proportion of pediatric patients with HIV RNA <400 c/mL (86%) at week 48 was numerically higher than, but comparable to adults who received emtricitabine as a component of a multiple-drug anti-HIV regimen for 48 weeks in studies FTC-301 and FTC-303 (78%). The overall rate for virologic failure was substantially higher in pediatric patients, 14% versus 5% in adult registration studies. In Study FTC-211 the number of virologic failures was comparable to the other two studies, but the higher rate compared to adults appears artificially inflated because of the small numbers of patients in the study. The actual reason(s) for virologic failure could not be determined since neither therapeutic drug monitoring or resistance testing was performed.

A total of 53/116 (46%) patients in study FTC-203 experienced a new CDC class event; only two were class C events: herpes simplex stomatitis and disseminated Mycobaterium tuberculosis. No new CDC events were reported in study FTC-211. Two patients in study FTC-202 experienced Mycobacterium avium complex infection.

In study FTC-203, the median increase in CD4 cells in naïve patients was +313/mm^3 (-512 to +1521) in naïve and -59.5 (-945 to +712) in treatment experienced patients. Since many of these patients were already on therapy with virologic suppression and increased CD4 counts, as great a CD4 cell count increase as naïve was not expected. The median change in percent CD4 cells reflected increases in both populations: +10.8% in naïve and +2.7% in experienced patients. Thus, considering the natural, age-related decline in CD4+ cells as all children mature, these changes in CD4+ T-lymphocytes are generally consistent with the age of maximum decrease in the count and percent of CD4+ T cells observed in healthy normal children.

Figures 2 and 3 show the overall median changes over time in CD4 counts and CD4% in studies FTC-203 and FTC-211.

Figure 2.

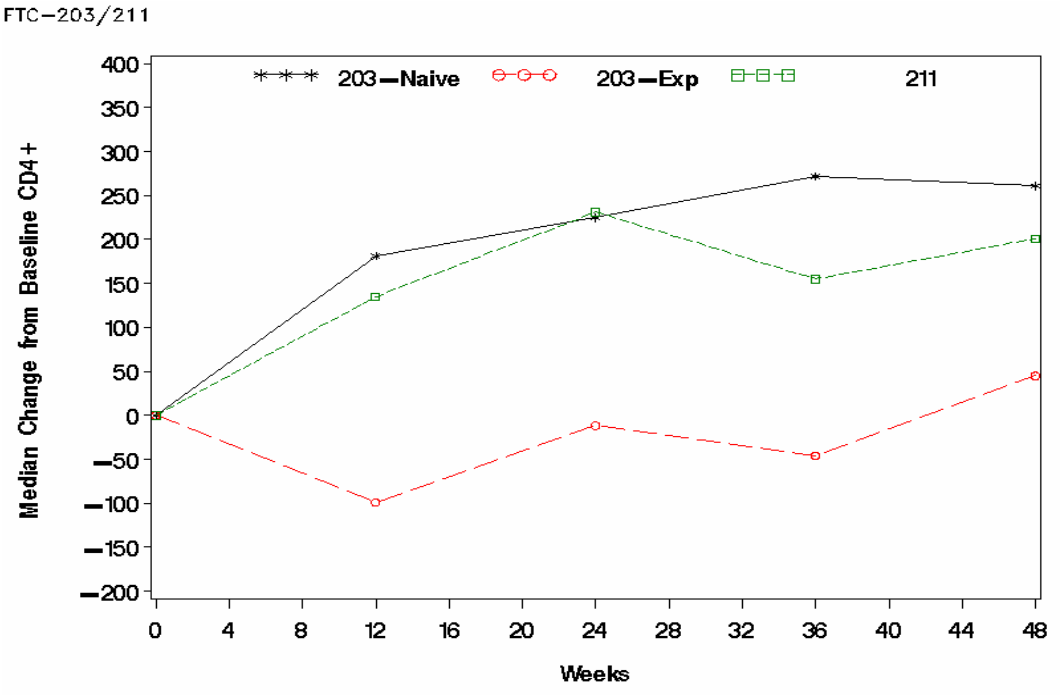
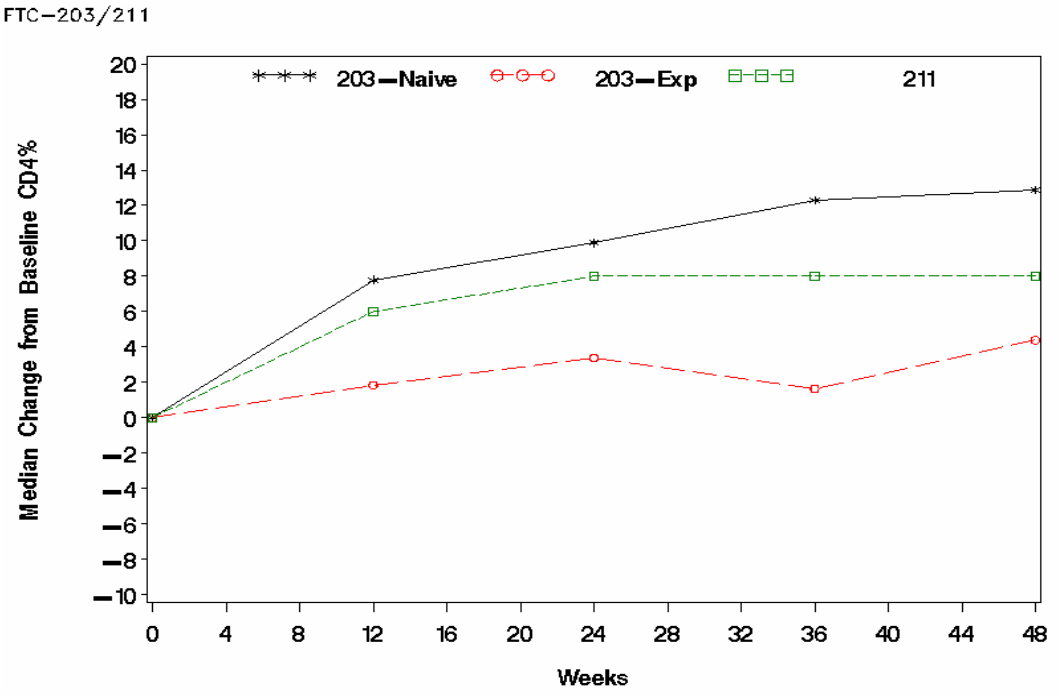


Figure 3.



Efficacy data from studies FTC-202 and FTC-203 suggests that ~80% of patients continued to respond to multiple-drug combinations containing emtricitabine at 96 weeks.

Due to the small number of HIV/HBV co-infected patients enrolled in any of the clinical studies, no analyses could be performed.

6.1.4 Clinical Microbiology

Resistance to emtricitabine appears rapidly due to emergence of the M184I/V mutation in the reverse transcriptase. Virology data was provided only for study FTC-203. In this study three of four treatment naïve patients who experienced virologic failure had evidence of the M184V mutation. Eight treatment experienced patients failed. At baseline four were unable to be genotyped and four had multiple mutations present. At the time of virologic failure, no new treatment emergent mutations were identified.

6.1.5 Efficacy Conclusions

The efficacy data support the conclusion that pediatric patients between 3 months and 18 years of age who were treated with Emtriva Oral Solution or Capsules as part of a multiple drug antiretroviral therapy combination attained antiviral and immunologic responses comparable to adult patients. Comparison of antiviral and immunologic response across age ranges yielded no significant differences between younger and older patients. Similarly, there were no significant differences between patients receiving the capsule or oral solution formulations.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Only one death was reported in the NDA. This death was reported in a 2 year-old black female who died of acute myeloblastic leukemia approximately one year after initiating FTC+d4T+Lopinavir/ritonavir in study FTC-203. It is unlikely this event was due to emtricitabine as it is not oncogenic.

7.1.2 Other Serious Adverse Events

Overall 33/166 (20%) patients experienced at least one serious adverse events. SAEs included: mumps, Grade 4 LFTs, nausea, asthenia and dizziness, decreased glucose, abdominal pain, elevated CPK (2), mild cervical dysplasia with HPV, rash with angioedema and diarrhea, anemia x 2, pancreatitis x 3, pneumonia x 7, hepatitis A x 4, accidental injury x 3, and pharyngitis x 3.

7.1.2.1 Dropouts and Other Significant Adverse Events
7.1.2.2 Overall profile of dropouts

Thirteen patients discontinued study medications prior to week 48: seven from study FTC-203, five from study FTC-202 (PACTG-1021), and one from study FTC-211.

One patient was enrolled in study FTC-203 and found not to be HIV-infected; he was discontinued from the study after receiving emtricitabine+d4T+LPV/r for 10 days. There was no report of adverse events in this patient. Other discontinuations from study FTC-203 included virologic failure (n=3), adverse events (n=2), and withdrawal of consent (n=2). The one discontinuation from study FTC-211 was a patient who withdrew consent and decided to no longer participate in the study; he had received only one dose of study medication. Two patients discontinued study FTC-202 due to rash, two due to virologic failure, and one withdrew consent for personal reasons (unable to adhere to the clinic visit schedule). There was no disease or demographic differences between patients who continued and those that discontinued from the three main clinical trials.

7.1.2.3 Adverse events associated with dropouts

Four patients discontinued the clinical studies due to adverse events: one each of anemia and pancreatitis, and two due to rash (one with angioedema) which resolved within 3 weeks after discontinuation of study medication.

In study FTC-0101 a 29 year old male healthy volunteer experienced Grade 2 ALT and Grade 1 AST after the second dose of emtricitabine which had not resolved by time he was lost to follow up; there was no increase in bilirubin.

7.1.2.4 Other significant adverse events

Grade 3 and 4 adverse events at least possibly related to study medications reported in the clinical trials included elevated GGT, dizziness, abdominal pain with headache and shortness of breath, elevated CPK, leucopenia, diarrhea with fever, and disseminated skin rash.

7.1.3 Other Search Strategies

No other search strategies were utilized.

7.1.4 Common Adverse Events

7.1.4.1 Eliciting adverse events data in the development program

Safety was generally evaluated by collection of adverse events (AEs) and HIV-1-related events, clinical laboratory testing (including hematology, clinical chemistry and urinalysis), physical examination, and vital signs measurements. AEs and HIV-1-related events were reviewed at each clinic visit. Clinical laboratory evaluations were performed at Screening, Baseline, and every 2-4 weeks to week 24, and then every 8 weeks from weeks 24 to 48. Physical examinations were performed at week 4 and then every 8 weeks from weeks 4 to 48. Vital signs were measured at every clinic visit.

In study FTC-202 (PACTG-1021) safety was evaluated by collection of adverse events, clinical laboratory data (including hematology, serum chemistry and urinalysis), pregnancy testing, and physical examination findings and vital signs measurements. Adverse events were reviewed at every clinic visit. All signs and symptoms $\geq$Grade 2, all central nervous system symptoms, and any grade of nausea, vomiting or abdominal pain associated with increased lipase or pancreatic amylase were recorded.

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

All adverse events reported in studies in which patients received at least one dose of emtricitabine were reviewed. In general, the review focused on known emtricitabine associated adverse events that occurred in adults and reviewed in the adult NDA.

7.1.4.3 Incidence of common adverse events

The adverse event profile of emtricitabine was well characterized in the large Phase 3 registration studies in adults. The most common events are listed in Table 5 below.

In Phase 1 pediatric studies, gastrointestinal events (abdominal pain, nausea), headache, and rhinitis were the most often reported adverse events; generally consistent with the known adverse event profile observed in adults.

The most frequent adverse events reported in the three clinical trials included: infection, fever, viral infection, abdominal pain, pain, rash, skin discoloration, leucopenia, and vomiting.

7.1.4.4 Common adverse event tables

Using a listing of the most common adverse events reported in adult studies of emtricitabine, the pediatric data were compared (see Table 5). With the exception of skin discoloration and vomiting the frequency of events occurring in pediatric patients was similar or less than the frequency reported in adults. Additionally, pediatric patients experienced more infections, fevers, pain, and gastroenteritis. Adverse events reported at >5% frequency will be included in the label.

Table 5. Treatment emergent adverse events reported in pediatric patients compared to adults[1]

	All Pediatric (n=169)	Adults (n=580)
Infection	44%	-
Fever	18%	-
Otitis media	23%	-
Pneumonia	15%	-
Abdominal pain	10%	8-14%
Myalgia	<1%	4-6%
Pain	7%	-
Asthenia	<1%	12-16%
Dizziness	<1%	4-25%
Rhinitis	20%	12-18%
Pharyngitis	2%	-
Nausea	1%	13-18%
Vomiting	23%	9%
Diarrhea	20%	23%
Gastroenteritis	11%	-
Hyperpigmentation[2]	32%	13%
Rash	21%	17-30%
Headache	1%	13-22%
Cough	28%	14%
Anemia	7%	-

1. Selected adverse events reported in ≥3% of patients in Emtriva pivotal studies FTC-301A and 303 (see Emtriva Prescribing Information).
2. Reported in 45/132 patients. (see below).

In study 203, the frequency of adverse events was higher among treatment naïve patients compared to those who had received 3TC prior to study entry. Since emtricitabine and 3TC are closely related, it is likely that patients who had received 3TC already experienced many of the adverse events compared to treatment naïve patients who received emtricitabine as part of their initial antiretroviral regimen; this phenomenon was consistent with adults in study FTC-303 (see NDA 21-500).

Vomiting and gastroenteritis were reported more frequently in pediatric patients. Almost all cases of vomiting occurred in study FTC-203. Thirty eight of 116 patients experienced at least one episode of vomiting; all were mild and self-limited, resolving spontaneously in 36/38, and none required dose modification or discontinuation. Most, 25/38, involved a singe episode of vomiting.

Acute gastroenteritis occurred in 22 patients and was coded as being a viral infection. All but two were graded as mild, and all resolved without need for dose modification or discontinuation. The higher frequency of vomiting and gastroenteritis may be attributable to the exposure of patients to viral diseases, e.g., South Africa, the concomitant use of protease inhibitors, mostly with ritonavir which is known to cause gastrointestinal adverse events. Patients with vomiting or gastroenteritis had similar antiviral efficacy compared to patients without these adverse events. Although higher than in adults, absorption of emtricitabine occurs within 1-2 hours of dosing, and given similar efficacy, it does not appear necessary to recommend re-dosing.

Longer term safety data from studies FTC-203 and FTC-202 did not demonstrate any new types of adverse events after 96 weeks of exposure to emtricitabine.

7.1.4.5 Identifying common and drug-related adverse events

Hyperpigmentation

Skin discoloration was reported in 13% (176/1348) of adult patients in the studies reviewed for approval of Emtriva Capsules. Skin discoloration was described as hyperpigmentation on the palms and soles, and it occurred predominantly in black patients. In the majority of cases, severity was assessed as mild, and no adult patients discontinued HIV studies due to this event. The mechanism and clinical significance of skin discoloration remains unknown, and is being further investigated in ongoing clinical studies in adults as post-marketing commitment.

Skin discoloration was reported in 45/116 and 0/16 patients in studies FTC-203 and 211 (overall 32%, 42/132). No cases were reported in FTC-202, but only Grade 2 or worse for signs and symptoms other than CNS events or those related to pancreatitis were to be reported. Three patients classified as having hyperpigmentation had other explanations for changes in skin color: hyperpigmentated burn scars, Café-au-lait spot, and ancanthosis nigricans; thus the final calculation of hyperpigmentation observed in pediatric studies was 32% (42/132).

The pattern of skin discoloration was similar to adults, affecting feet and or hands, rarely the tongue, nails and lips. All cases were asymptomatic; only one was graded as moderate (Grade 2). Thirty-nine patients resided in South Africa and six were located in the US. All but one patient was of black African descent. No patient discontinued study medications due to skin discoloration. Sixteen had resolution, some resolutions with recurrence on other body areas, and 2/4 that discontinued for other reasons had skin discoloration present at the time of discontinuation; both experienced resolution of skin discoloration off therapy. The one patient who died in study FTC-203 had hyperpigmentation noted at time of death (see above).

According to the applicant, living in South Africa appears to be the biggest predictor for hyperpigmentation. However, since the majority of patients in the South African trial were black, it is not possible to determine the contribution of race without other broader representation of other races within South Africa; it is unlikely this information will be produced given that there are few children of other races being treated with antiretroviral therapy in South Africa.

Unfortunately, it does not appear that patients were assessed by a dermatologist or that any investigation into the mechanism or reversibility was conducted.

In summary, the frequency of hyperpigmentation in pediatric patients was 32% (42/132), which is still substantially higher than the frequency observed in adult clinical trials. The frequency of hyperpigmentation among pediatric patients will be highlighted in the Emtriva Oral Solution and Tablet labels, and the applicant will continue to assess patients who experience changes in skin color to determine mechanism of action and reversibility.

7.1.5 Laboratory Findings

Overall the frequency of Grade 3 and 4 laboratory abnormalities in the pediatric trials is comparable to the types and frequencies observed in adult trials. Across the three clinical studies, 16 (9%) patients experienced at least one Grade 3 and/or 4 laboratory abnormalities. The abnormalities included: amylase >2 x ULN (n=4), neutrophils <750/mm^3 (n=3), CPK >4 x ULN (n=2), ALT >5 x ULN (n=2, %), and one event each of bilirubin >3 x ULN, GGT >10 x ULN, glucose <40 mg/dL, lipase >2.5 x ULN, and hemoglobin <7 g/dL.

Two patients in study FTC-203, a 28 month old black female and a 2 year old black male, experienced Grade 4 AST and ALT and Grade 3 bilirubin elevations associated with an episode of acute Hepatitis A. In both cases study medications were interrupted, liver functions returned to normal once the Hepatitis resolved, and study medications were restarted without sequelae.

Table 6 provides the frequency of laboratory abnormalities, all grades, reported in the pediatric database.

Table 6. Treatment emergent laboratory abnormalities, all grades

	FTC-203 (n=116)	**FTC-202 (n=37)**	**FTC-211 (n=16)**
Glucose abnormalities	60 (52%)		
↓Sodium		19 (51%)	
↓Hemoglobin	33 (28%)	13 (35%)	
↓Potassium		12 (32%)	
↑Lipase	7 (6%)		
↑Amylase	6 (5%)		8 (50%)
↑Alk phos	3 (3%)	14 (38%)	10 (63%)
↑Bilirubin	8 (7%)		
↑AST/SGOT	19 (16%)	23 (62%)	5 (31%)
↑ALT/SGPT	15 (13%)	11 (30%)	4 (25%)
↑Creatinine		19 (51%)	
↑Triglycerides	61 (53%)	30 (81%)	8 (50%)
↑CPK		10 (27%)	
↑Cholesterol	51 (44%)	21 (62%)	11 (69%)
↓Platelets	1 (<1%)		
↓Neutrophils	41 (35%)		7 (44%)

7.1.5.1 Overview of laboratory testing in the development program

All laboratory assessments, except viral genotyping and laboratory assessments that had to be performed at a local laboratory (e.g., arterial blood gases), were typically performed by a contract central laboratory designated by the applicant, to ensure standardization of results.

It is difficult to determine the absolute contribution of emtricitabine to laboratory abnormalities because emtricitabine was a component of triple drug regimens, and no comparator arms were utilized in any of the clinical trials.

7.1.5.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable, as all clinical studies were single arm and non-comparative.

7.1.5.3 Standard analyses and explorations of laboratory data

No trends or patterns in serum chemistry, hematology, or urinalysis parameters were identified.

7.1.6 Vital Signs

In general, there were no significant changes in vital signs identified.

7.1.7 Human Carcinogenicity

Recently completed non-clinical carcinogenicity studies demonstrate that emtricitabine is not oncogenic.

7.1.8 Special Safety Studies

Propylene Glycol

As noted in the CMC section, at the maximum recommended dose of 6 mg/kg/day (240 mg/day maximum), patients would receive approximately (b) (4) of propylene glycol; substantially below the World Health Organization's recommended limit of (b) (4)/day.

The emtricitabine clinical program provides experience with emtricitabine in combination with Kaletra. In Study FTC-203 emtricitabine oral solution was administered to 70 treatment-naïve children aged 0.3 to 12 years in combination with stavudine (d4T) and Kaletra. Stavudine contains no propylene glycol, but Kaletra (80 mg lopinavir [LPV]/mL and 20 mg ritonavir [RTV]/mL) contains (b) (4) propylene glycol. The Kaletra pediatric dosage of 12/3 mg/kg BID for patients 7 to < 15 kg and 10/2.5 mg/kg BID for patients 15 to 40 kg corresponds to a dose of propylene glycol of (b) (4) BID and (b) (4) BID respectively, *i.e.*, a daily dosage of 45.8 mg/kg for children (b) (4) for children up to 40 kg. If given with emtricitabine, the total daily propylene glycol exposure in patients weighing <15 kg could be as much as (b) (4)/day (b) (4) from Kaletra and (b) (4) from emtricitabine).

In patients in FTC-203, there were no reports of hyperosmolality, central nervous system depression, or other events possibly attributable to propylene glycol, which would constitute a safety signal clearly disparate from the adult safety profile. At this time it is not possible to provide specific advice to clinicians about how to calculate total daily exposure to propylene glycol as the concentrations of propylene glycol in the formulations of other medications that might be used with emtricitabine oral solution are not readily available.

Gender and Race Assessments

Analyses conducted by the applicant revealed no clinically relevance differences in safety between Black and non-Black patients or between genders. Review of these analyses by the Statistical Reviewer, Dr. Zhou, confirmed the applicant's assessment.

7.1.9 Withdrawal Phenomena and/or Abuse Potential

There is no withdrawal phenomenon or abuse potential with emtricitabine.

7.1.9 Human Reproduction and Pregnancy Data

Emtricitabine is classified as Pregnancy Category B. There are no data on use of emtricitabine during pregnancy. To monitor fetal outcomes of pregnant women exposed to emtricitabine, an

Antiretroviral Pregnancy Registry has been established, and healthcare providers are encouraged to register patients; this will be included in the Emtriva Oral Solution label.

An interim analysis from the Antiretroviral Pregnancy Registry issued in December 2004 reported a total of 16 first trimester exposure to emtricitabine and 1 second/third trimester exposures; no birth defects were reported in these 17 pregnancy reports. However, no conclusions could be drawn for emtricitabine as there are insufficient cases to compare the prevalence of birth defects to the general population.

7.1.10 Assessment of Effect on Growth

In Study FTC-203 and FTC-211, measurements of height and weight were taken at study entry (screening, Baseline), at Week 2 and Week 4, and every 4 weeks thereafter through Week 48, and every 12 weeks thereafter. The protocol did not specify a standard method for collection of height and weight measurements. We analyzed the change from Baseline at Week 48 for height (cm) and weight (kg) to assess changes in growth and development. Overall, the change from Baseline in height (cm) and weight (kg) by age group showed a gradual weight and height gain through Week 48 in both studies up to a median [range] change of +1.8 [-4.7-7.4] kg and +6 [-3.0-27.5] cm, and +4.5 [0.5-21.5] kg and +6 [1.0-10.0] cm at Week 48, respectively in FTC-203 and FTC-211 study.

Because there was no control group of either healthy pediatric subjects or HIV-1-infected pediatric patients not on antiviral therapy, it is not possible to determine if administration of emtricitabine-based HAART had a beneficial effect on growth and development.

7.1.11 Overdose Experience

There is no information on overdoses in pediatric patients. The Emtriva Capsule labeling states: "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." This information will be included in the Emtriva Oral Solution label.

7.1.12 Post marketing Experience

Emtricitabine has been marketed for treatment of HIV-1 infected adults in the US since 2003 as Emtriva and since August 2, 2004 as a component of the fixed-dose combination Truvada. Periodic Safety Update Reports were reviewed representing over 30,000 patient years of treatment. No new adverse events or patterns of adverse events related to emtricitabine have been identified.

7.2 Adequacy of Patient Exposure and Safety Assessments

The number of pediatric patients and duration of treatment with emtricitabine represents a robust database upon which to determine safety and efficacy. The study types, designs, demographics, extent of exposure, postmarketing experience, adequacy of clinical experience, and clinical testing have been summarized above, and support the safety findings.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing of Emtriva® Oral Solution is 6 mg/kg/day (maximum 240 mg/day) administered once daily without regard to food intake. Pediatric patients who weigh >33 kg and who can tolerate a capsule could take a 200 mg Emtriva Capsule once daily. Adults could also use the oral solution and the dosing would be 240 mg/day. These doses and regimen are supported by both clinical pharmacology studies and clinical trials data as reviewed above. Adults who require dose reductions for renal impairment could also use the oral solution.

8.2 Drug-Drug Interactions

Drug-drug interactions have been well characterized and important interactions are summarized in the Emtriva label.

8.3 Special Populations

Emtricitabine is not metabolized by hepatic enzymes. Therefore, the impact of liver impairment on the pharmacokinetics of emtricitabine is limited.

With respect to use of emtricitabine in adult patients with renal impairment, pharmacokinetic data submitted in this NDA provided an opportunity to estimate dosing of the oral solution. A renal impairment study conducted in adults showed that emtricitabine capsules be administered every two to four days based on the patient's creatinine clearance. Pharmacokinetic data now support administration of emtricitabine oral solution on a daily basis to adults with renal impairment, again based on creatinine clearance. A renal impairment study in pediatric patients would be extremely difficult to conduct as it would be unlikely for a sponsor to identify a sufficient number of patients with renal impairment. However, based on the adult data, dosing in pediatric patients with renal impairment could follow similar dose adjustments. The following table will be included in the Emtriva labeling:

Table 7. Dose Adjustment in Adult Patients with Renal Impairment

Formulation	> 50 mL/min	30-49mL/min	29-15 mL/min	< 15-mL/min or on hemodialysis
Capsule	200-mg QD	200-mg Q48H	200-mg Q72H	200-mg Q96H
Oral Solution	240-mg QD (24 mL)	120-mg QD (12 mL)	80-mg QD (8 mL)	60-mg QD (6 mL)

8.4 Pediatrics

This is a pediatric NDA and all the above information applies primarily to pediatric patients.

8.5 Advisory Committee Meeting

No Advisory Committee was necessary for this application.

8.6 Postmarketing Risk Management Plan

Emtriva Capsules have been marketed in the US since October 2002. No post-marketing safety issues have been identified, and no new post-marketing risk management plan is necessary for the oral solution.

9 OVERALL ASSESSMENT

9.1 Conclusions

Based on the safety, pharmacokinetic and antiviral activity reviewed in this NDA, the application is recommended for approval. Clinical pharmacokinetic, safety and efficacy data from 169 HIV-1 infected pediatric patients aged 3 months to 17 years treated with Emtriva® Oral Solution or Emtriva® Capsules in combination with other antiretroviral agents for at least 48 weeks (naïve versus experienced) demonstrated comparable exposures (e.g., AUC), general safety profile and efficacy (proportion with HIV RNA <400 c/mL and increases in CD4 cell counts) in pediatric compared to adult patients.

Hyperpigmentation, manifested as skin discoloration on the palms and soles, occurred substantially more frequently in pediatric patients (34%) compared to adults (13%); although the etiology remains under investigations, all cases appeared mild with resolution upon discontinuation of dosing.

Patients receiving emtricitabine oral solution with other drugs containing propylene glycol in their formulation may be at risk for propylene glycol-related toxicities; but it is not possible to quantify this risk at this time as the concentration of propylene glycol in other medications that might be used with emtricitabine oral solution are not readily available.

With respect use of emtricitabine in patients with renal impairment, pharmacokinetic data submitted in this NDA provided an opportunity to estimate dosing of the oral solution in adult patients with varying degrees of renal impairment.

9.2 Recommendation on Regulatory Action

From a clinical perspective, the NDA for Emtriva® Oral Solution should be approved.

9.3 Recommendation on Postmarketing Actions

- The Applicant is continuing to assess the mechanism of action and clinical significance of hyperpigmentation.
- To address the requirements of PREA, the Applicant has committed to submit the results of an ongoing study of the pharmacokinetics, safety and antiviral activity of emtricitabine in patients 0 (birth) to 3 months of age. The report of this study is due in March 2006.

9.3.1 Risk Management Activity

Emtriva Capsules are currently available as a sole agent and as a component of the fixed-dose combination known as Truvada. The capsule labeling adequately describes the Warnings, Contraindications and Precautions related to emtricitabine. As such, no additional post-approval risk management activities are required.

9.3.2 Required Phase 4 Commitments

There are no new required Phase 4 requests.

9.3.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

9.4 Labeling Review

The Emtriva Capsule label will be revised to include salient information about the new oral solution formulation including pediatric pharmacokinetic, efficacy and safety data with a specific discussion of the higher frequency of hyperpigmentation observed in pediatric patients compared to adults. A section describing the renal dosing of emtricitabine oral solution will also be included in the product labeling.

9.5 Comments to Applicant

There are no comments to be conveyed to the applicant.

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

/s/

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9/23/2005 09:34:16 AM
MEDICAL OFFICER

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